The American Journal of Medicine

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The American Journal of Medicine

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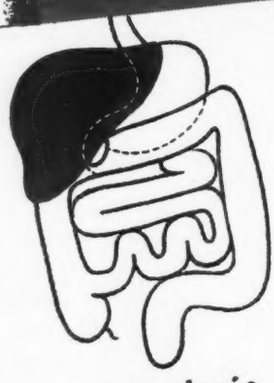

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Analysis of Sequential Physiologic Derangements in Epidemic Hemorrhagic Fever. With a Commentary on Management . . . . . DAVID P. EARLE 690

Under the able Guest Editorship of Dr. David P. Earle, who was himself responsible for many of the studies cited, the *Journal* brings together in this symposium a large body of data on epidemic hemorrhagic fever collected at the Hemorrhagic Fever Center (48th Surgical Hospital, Mobile Army) in Korea. While the disease is limited to a remote area, it is, by virtue of its extraordinary characteristics, of very general interest from many points of view. For, encompassed within a brief course, are such violent fluctuations in a variety of physiologic adjustments that hitherto subtle and obscure relationships are easily apprehended and unsuspected meanings in other, more familiar diseases take on new significance. As examples, one might cite the violent redistribution of water and electrolytes in the several phases of the disease, and the unequivocal indication of gross capillary leakage, a much disputed complication in other circumstances. There is much to think about in these papers.

End of Symposium on Epidemic Hemorrhagic Fever

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Viral Hepatitis. Problems and Progress to 1954 . . . . . JOHN R. NEEFE 710

Dr. Neefe, in this splendid review, brings together current information regarding hepatitis due to infections by virus IH and virus SH. After pointing out the difficulties confronting investigators because of failure to find an animal host other than man, he goes on to discuss what is known about etiology, epidemiology, questions of immunity, clinical manifestations and complications, laboratory findings, the carrier state, diagnosis, prevention and treatment. Of special interest is the difficult analysis of the unduly protracted course and the revision of views as to time of ambulation.

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One has but to read the extraordinary history of this case prior to recognition of vitamin A intoxication as the principal factor in pathogenesis to appreciate the importance of familiarity with the skin, bone and nervous system manifestations of chronic vitamin A overdosage in the adult. A well known syndrome in the infant, the condition has not been sufficiently recognized in self-medicating adults. It is hoped that this interesting report will facilitate wider appreciation of the nature of the hazards of chronic vitamin A poisoning in man.

Atypical Amyloidosis and Bone Marrow Plasmacytosis in a Case of Hypersensitivity to Sulfonamides . . . . . JULIUS WOLF AND BARNEY WORKEN 746

A case report of unusual interest, describing the clinical and autopsy findings in a patient who presented widespread atypical amyloidosis, hyperglobulinemia and bone marrow plasmacytosis not due to multiple myeloma but attributed to sulfonamide hypersensitivity. Such cases, which are probably not as rare as the paucity of reports would seem to indicate, offer many points for speculation.

Hypothromboplastinemia Associated with a Circulating Anticoagulant and Hemorrhagic Diathesis . . . . . MICHAEL S. BRUNO AND HERBERT S. BRODY 756

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Tuberous Sclerosis. Report of a Case with Unusual Pulmonary Manifestations
CHARLES M. SILVERSTEIN AND GEORGE L. MITCHELL, JR. 764

A case report of unusual interest, indicating that tuberous sclerosis may present with pulmonary involvement characterized by a peculiar form of diffuse cystic lung disease and recurrent pneumothorax.

Advertising Index on 3rd Cover

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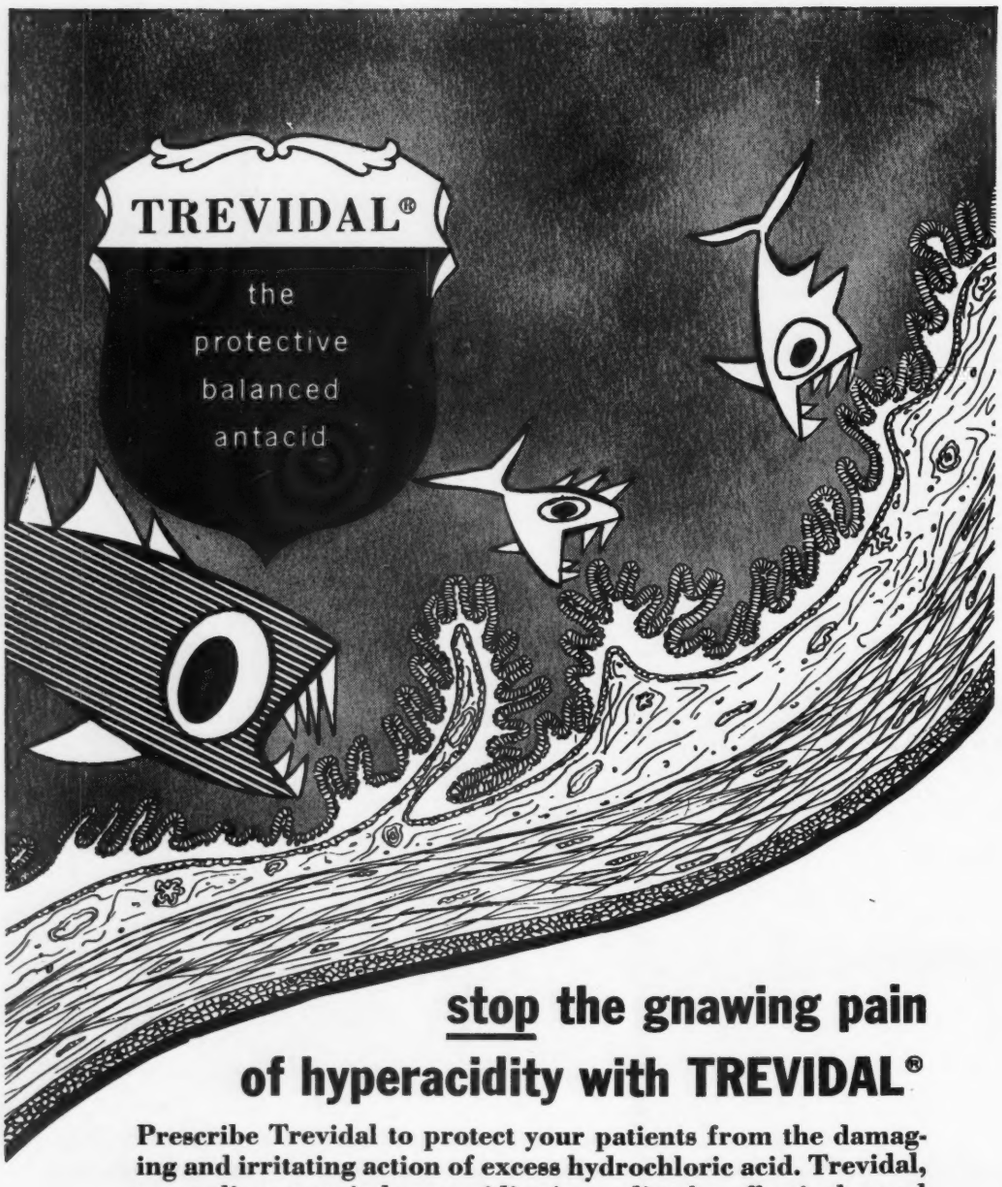

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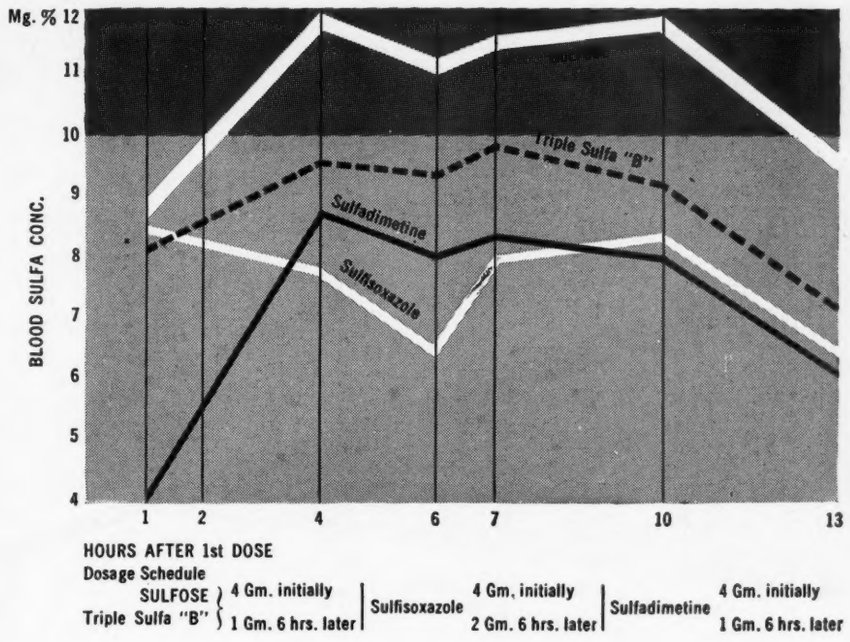

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1. Berkowitz, D.: Antibiot. & Chem. *3*:618 (June) 1953. 2. Jawetz, E.: California Med. *79*:99 (Aug.) 1953. 3. Cecil, R. L., and Loeb, R. F.: Textbook of Medicine, W. B. Saunders Co., Philadelphia, 1951, pp. 963-967. 4. Sophian, L. H., and others: The Sulfapyrimidines, Press of A. Colish, New York, 1952.

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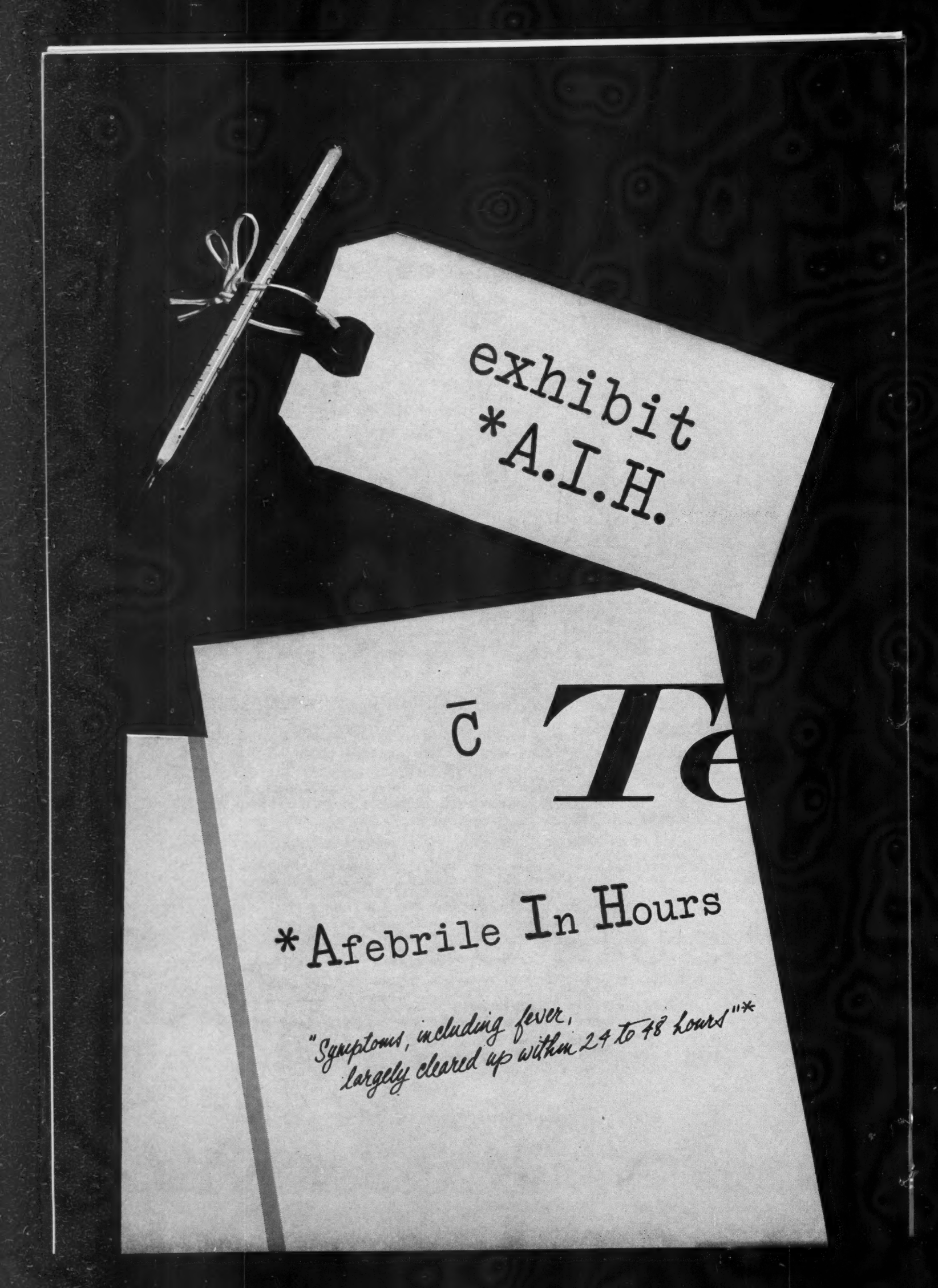
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******English, A. R., et al.: Antibiotics Annual (1953-1954), New York, Medical Encyclopedia, Inc., 1953, p. 70.*

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1. Proc. Staff Meet. Mayo Clin. 21:497, 504, 1946.
2. J. Clin. Endocrinol. Metab. 12:454, 1952.
3. Journal-Lancet 70:192, 1950.

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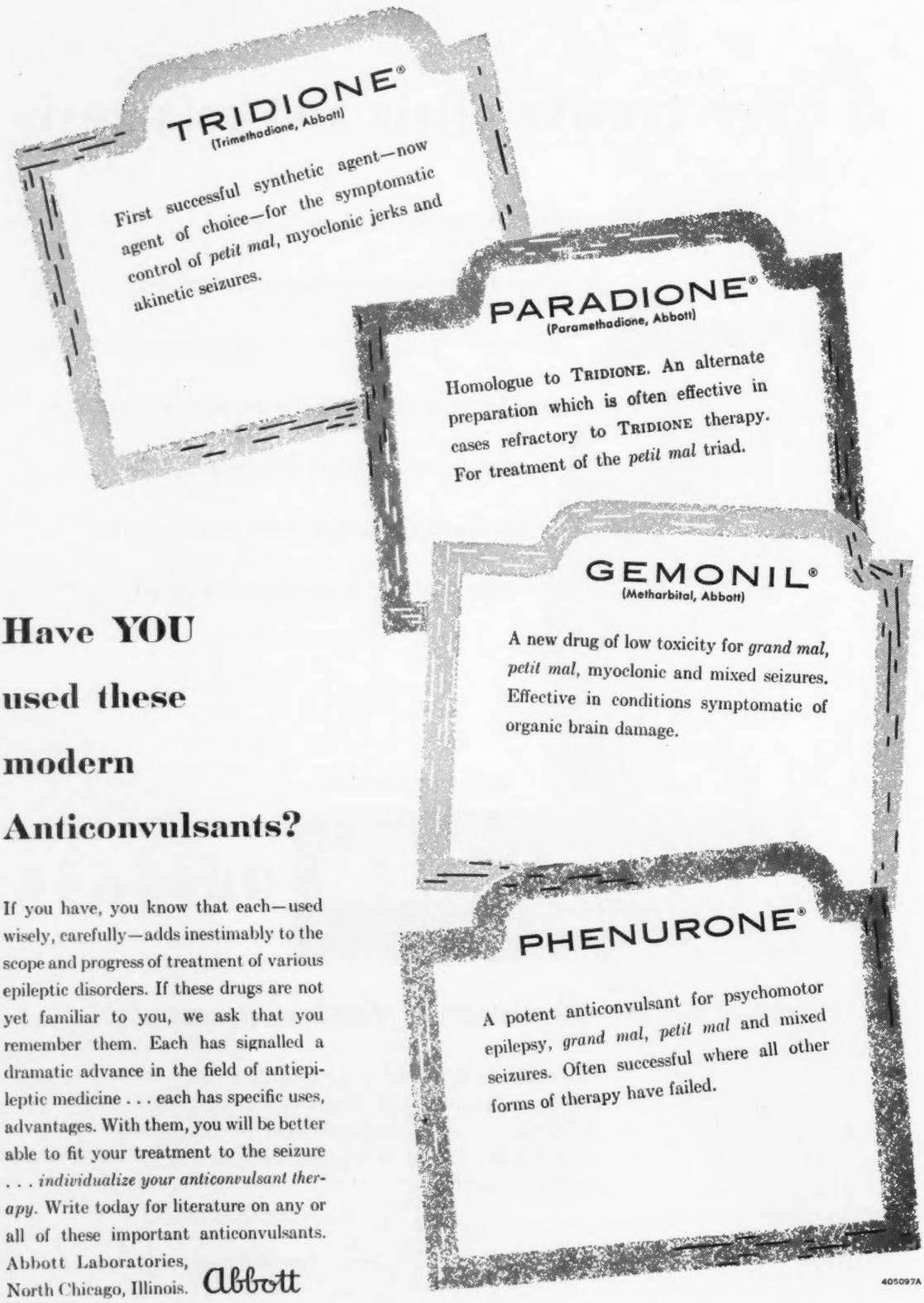

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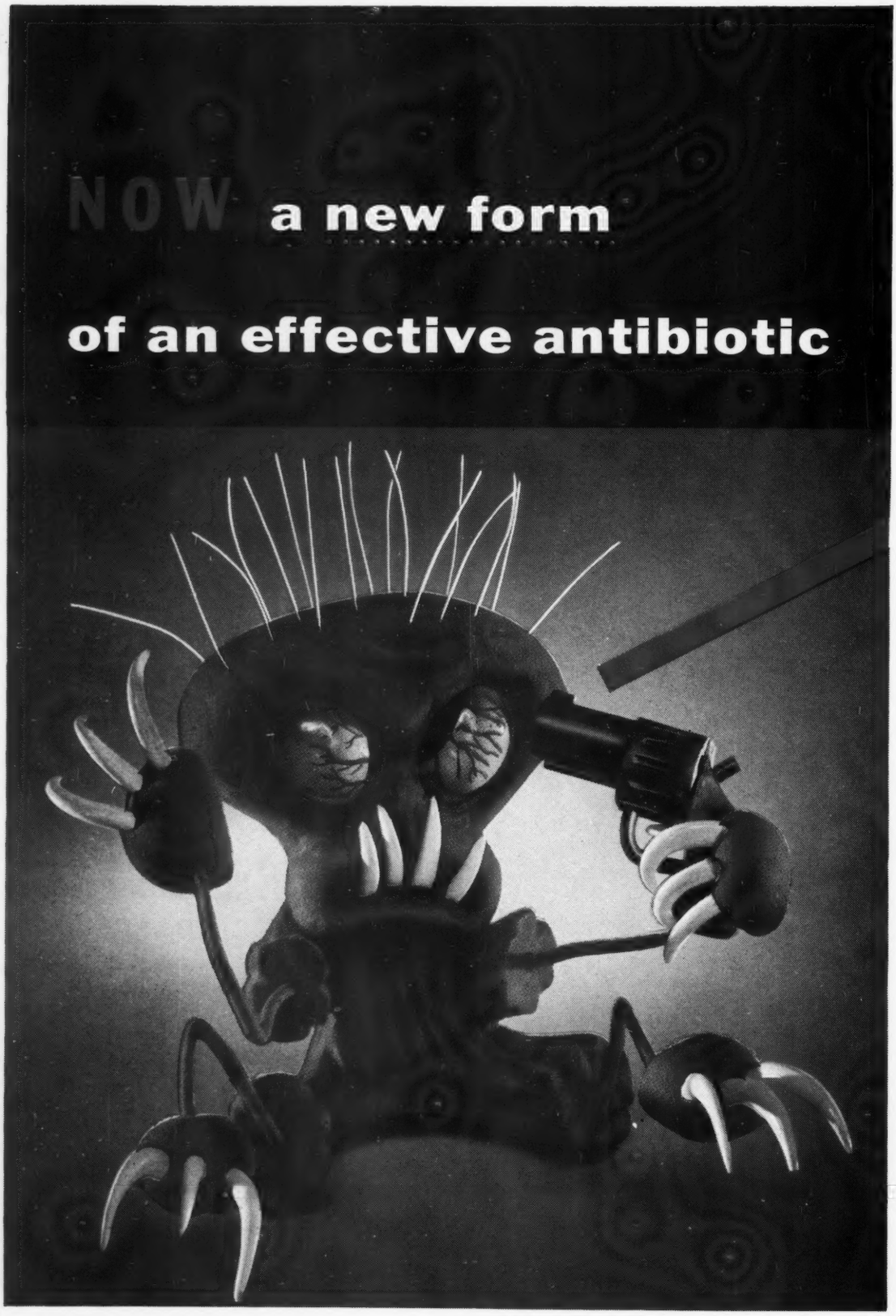
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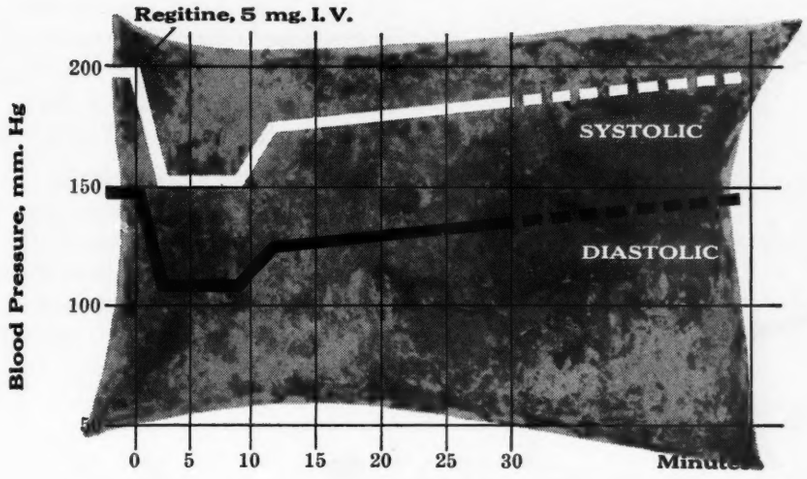

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1. DECOURCY, J. L.: AM. J. SURG., 86:37, JULY, 1953

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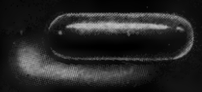

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May, P. R. A., and Ebaugh, F. G.: Use of Hypnotics in Aging and Senile Patients: A Clinical Study of Dormison, J.A.M.A. 152:801, 1953.

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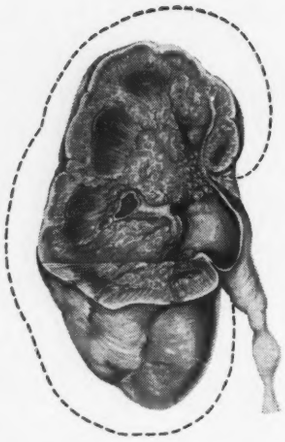

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Pyridoxine Hydrochloride	1 mg.
Vitamin B_{12}	2 mcg.
Pantothenic Acid (as calcium pantothenate)	10 mg.
Liver Fraction 2, N.F.	0.3 Gm. (5 grs.)
Brewer's Yeast, Dried	0.15 Gm. (2½ grs.)

Sur-bex with C **contains 150 mg. of ascorbic acid in addition to the vitamin B complex factors above.**

...or SUR-BEX WITH VITAMIN C

Rauwolfia serpentina

AS SOLE THERAPY

For every patient with mild, moderate, or labile hypertension

In addition to dropping the blood pressure moderately, Rauwolfia serpentina produces marked, often dramatic, subjective improvement. It relaxes the emotionally tense patient, gradually inducing a welcome state of calm tranquility.

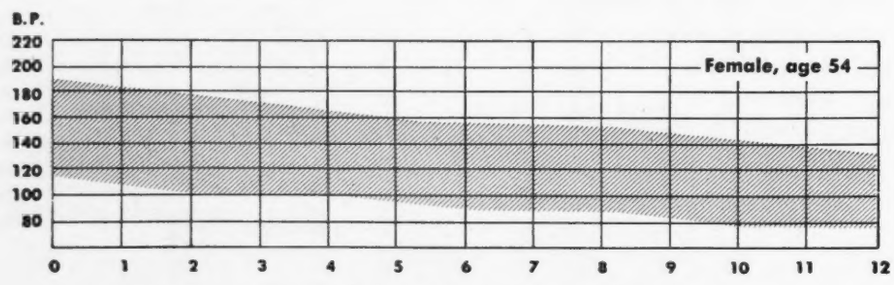
Headache, tinnitus and dizziness are greatly relieved, and the discomfort of palpitation is usually overcome. Hence, it usually suffices as sole medication in mild, moderate and labile hypertension, especially when the emotional element is a prominent factor.

Rautensin

Purified Rauwolfia Serpentina Alkaloids

Rautensin produces the typical hypotensive, sedative, and bradycrotic effects characteristic of this important new drug. Each tablet contains 2 mg. of the alseroxylon fraction, a highly purified alkaloidal extract entirely free of inert material. The alseroxylon fraction is tested in dogs for its ability to lower blood pressure, produce sedation, slow the pulse.

The initial dose of Rautensin is 2 tablets (4 mg.) daily for 30 to 60 days. After the full therapeutic effect has been established, the daily intake is dropped to 1 tablet (2 mg.) daily. Side actions are rare and there are no known contraindications.



Weeks of therapy. Rautensin, 4 mg. daily. Marked subjective improvement.

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Rauwolfia serpentina
IN COMBINATION

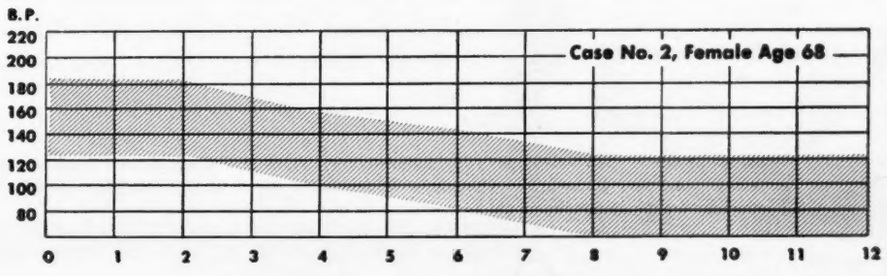
For the patient with chronic, severe, or fixed hypertension

Most cardiologists today assert that in severe or fixed essential hypertension, combination therapy is more efficacious than any single drug alone. The combination of Rauwolfia serpentina and Veratrum viride is especially favored since it results in an additive, if not a synergistic, effect. In this combination, the dosage requirements of veratrum are significantly reduced, hence the incidence of side effects is greatly minimized.

Rauvera
Rauwolfia Serpentina and Veratrum Viride Alkaloids

Each Rauvera tablet combines 1 mg. of the alseroxylon fraction of Rauwolfia serpentina and 3 mg. of alkavervir, a highly purified alkaloidal extract of Veratrum viride. The potent hypotensive action of veratrum is thus superimposed on the desirable influence of Rauwolfia. Rauvera leads to a substantial reduction in blood pressure and marked subjective improvement, hence produces excellent results in chronic, severe, and fixed essential hypertension.

The average dose of Rauvera is 1 tablet 3 times daily, after meals, at intervals of no less than 4 hours.



Weeks of therapy. Rauvera, 4 tablets daily. Note blood pressure response.

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SANBORN SPECIALIZES. Sanborn's *primary* and *major* interest in the medical field for the past 35 years has been the design, manufacture, and servicing of electrocardiographs. Sanborn men can therefore *concentrate* on your interest in this type of equipment.

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'Dicurin Procaine'

(Merethoxylline Procaine with Theophylline, Lilly)

ready to use • stable • painless on injection

FORMULA:

Each cc. contains 100 mg. of 'Dicurin Procaine' (equivalent to 39.3 mg. of mercury and 45 mg. of procaine base) and 50 mg. of anhydrous theophylline.

DOSAGE RANGE:

0.5 to 2 cc. daily as required. May be given subcutaneously (deep), intramuscularly, or intravenously.

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The American Journal of Medicine

VOL. XVI MAY, 1954 No. 5

Foreword

BEGINNING in June, 1951, United Nations' troops in Korea encountered an acute disease characterized by fever, prostration, vomiting, a variety of hemorrhagic manifestations, shock, proteinuria and renal failure. The first few patients had been treated recently for malaria with chloroquine but an unusual reaction to this drug was soon eliminated as a cause for the clinical manifestations, as was leptospirosis (Weil's disease) which has several obvious similarities.

However, a disease known to the Japanese as epidemic hemorrhagic fever and to the Russians as epidemic hemorrhagic nephroso-nephritis or Far Eastern Hemorrhagic Fever,* had been described in two U. S. Army technical bulletins on Korea and Manchuria (TB MED 208, 1945 and TB MED 216, 1946). Captain John Craig, M.C., Preventive Medicine Officer of the U. S. X Corps., in the fall of 1950 requested that further information on this disease be obtained from Japanese sources, and in 1951 he compiled a brief summary of this material. Captain Ralph M. Takami then translated a number of Japanese medical articles on the disease, interviewed several Japanese investigators who had worked with it, and prepared a review of the subject which was distributed to medical personnel throughout the Far East Command. Based on this information, and as more and more cases developed, it was soon recognized that this unusual clinical syndrome was indeed epidemic hemorrhagic fever. A summary of information on the disease available through 1952 has been published in a U. S. Army technical bulletin (TB MED 240, 1953).

This disease was apparently first described by the Russians who encountered it in Far Eastern Siberia in the middle 1930's. Russian investigators in a series of well planned studies demonstrated that the disease could be reproduced in human volunteers by the intravenous administration of blood or urine obtained from patients up to but not after the fifth day of illness. Serial passage in humans was also obtained. They further found that the incubation period was generally ten to fifteen days, that a single attack conferred immunity and that the disease-producing agent would pass through a size N Berkefeld filter. However, the Russians were unable to establish the disease in experimental animals. Closely parallel results were obtained by Japanese workers in experiments conducted independently at the same time. More extensive American efforts to transmit hemorrhagic fever to a wide variety of possible experimental hosts, including tissue cultures, likewise have failed. Nor has it been possible as yet to develop specific diagnostic tests.

Study of the mode of transmission of hemorrhagic fever has been handicapped by the inability to establish the disease in experimental animals. Nevertheless, extensive and interesting entomologic[2] and epidemiologic[3] observations suggest that hemorrhagic fever may be transmitted to man by rodent ectoparasites such as fleas, mites, ticks and chiggers. Of these, chiggers seem best to fit the observed epidemiologic facts.

* A considerable literature on epidemic hemorrhagic fever exists in the Russian and Japanese languages. However, because of inaccessability of these papers, references in this symposium are limited to those in English. A bibliography of world literature on epidemic hemorrhagic fever is available in an excellent monograph.[1] This reviews available literature not only on epidemic or Far Eastern hemorrhagic fever but also on four other separate and distinct hemorrhagic fevers that occur in Russia. The Russians report that some of these are tick-borne virus diseases.

[1] GAJDUSEK, D. C. Acute infectious hemorrhagic fevers and mycotoxicoses in the Union of Soviet Socialist Republics. Medical Science Publication 2, Walter Reed Army Medical Center, Washington, D. C., May, 1953.

[2] TRAUB, R., HERTIG, M., LAWRENCE, W. H. and HARRISS, T. T. Potential vectors and reservoirs of hemorrhagic fever in Korea. Submitted for publication in *Am. J. Hygiene.*

[3] GAULD, R. L. and CRAIG, J. P. Epidemiological pattern of localized outbreaks of epidemic hemorrhagic fever. *Am. J. Hygiene*, 59: 32, 1954.

Prior to the recent military campaigns in Korea, cases of hemorrhagic fever had been reported only in the drainage area of the Amur River which separates Far Eastern Siberia from Manchuria. It is not known whether the disease existed unrecognized in Korea prior to 1951 or whether it spread to Korea secondary to the recent military campaigns. So far, the vast majority of cases in Korea have been contracted north of the 38th parallel, with practically no cases reported south of the city of Seoul and the Han River. The natural reservoir of hemorrhagic fever is thought to be one or more types of field rodents, such as field mice, voles and hamsters.

Although the mode of transmission of hemorrhagic fever is not definitely known, the circumstantial evidence cited warranted a trial of control measures that had proved effective in scrub typhus, a disease which is transmitted by chiggers. There has been a substantial decrease in the number of cases of hemorrhagic fever in Korea, following the institution of such measures, except during the fall of 1953 when there was a slight increase over the preceding spring outbreak. It is not yet known whether the decreased incidence should be attributed to the control measures or to natural phenomena.

The clinical manifestations of hemorrhagic fever are numerous, varied and follow one another in rapid and confusing sequence. In April, 1952, a special Hemorrhagic Fever Center (8228th Mobile Army Surgical Hospital) was set up near the area where the majority of cases were occurring among the U. S. troops. This hospital was moved to a semi-permanent type of installation in the outskirts of Seoul in the late fall of 1952 and was redesignated the 48th Surgical Hospital (Mobile Army). Almost all suspected cases were evacuated to the Hemorrhagic Fever Center by helicopter. This afforded an excellent arrangement for the careful study of this disease. Accordingly, a number of studies were initiated by the medical officers of the Hemorrhagic Fever Hospital and by visiting teams of investigators. The results of many but not all of these studies are reported in the various papers of this symposium. It should be appreciated that these studies were initiated under field conditions in a mobile tent hospital and were carried out for the most part during an epidemic by medical officers who were responsible for the care of a heavy load of seriously ill patients often requiring almost constant medical attention. Despite this, and despite many practical difficulties such as the problem of obtaining stable electric current from field equipment for scientific instruments, a remarkable body of data was collected over the few months of the fall 1952 epidemic.

Many of these studies would have been impossible without the unstinting assistance of the nursing staff and of the medical corpsmen, both in the laboratory and on the wards. All the authors of this symposium join in expressing their gratitude and admiration for the many ways in which material assistance and sound and fruitful advice and guidance were given by the medical departments of the 8th Army and the Far East Command, by the 406th Medical General Laboratory in Tokyo, the Army Medical Service Graduate School and the Commission on Hemorrhagic Fever.

There are probably few if any acute infectious diseases which require greater attention to physiologic disturbances than epidemic hemorrhagic fever, nor in which close and thoughtful medical observation and devoted nursing care are more important; the degree to which these qualities were apparent at the Hemorrhagic Fever Hospital was most impressive and stimulating, for no specific treatment for hemorrhagic fever has been found to date. Convalescent serum and whole blood, and a variety of antibiotics and other agents have had little or no beneficial effects.

It will be noted that hemorrhagic fever occurs in a rather limited geographical area. Hence very few Western physicians will have occasion to treat patients with this disease. Nevertheless, as will be apparent from study of this symposium, a number of lessons applicable to other, more familiar diseases may be drawn from a study of hemorrhagic fever. The many and varied physiologic and biochemical derangements characteristic of hemorrhagic fever, together with the unique pathologic findings, have more general implications. They have already suggested a number of concepts regarding mechanisms of disease that probably operate in more commonly encountered disorders where, however, they are too subtle or too infrequent to have demanded formulation and study hitherto.

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Symposium on Epidemic Hemorrhagic Fever

The Clinical Course of Epidemic Hemorrhagic Fever*

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More than 1,000 cases of epidemic hemorrhagic fever, one of a group of severe febrile illnesses previously described by Russian and Japanese physicians but unfamiliar to Western medicine, occurred among the United Nations forces in Korea during the fall of 1951.[1–5] A special hospital was established in Korea the following spring for more intensive investigation and treatment of patients with this disease. In the spring 1952 outbreak 613 cases were hospitalized for study. Clinical observations on these patients formed the background for more detailed investigation of 264 patients with hemorrhagic fever admitted in the outbreak occurring in the fall of 1952. The purpose of this report is to describe the clinical course of hemorrhagic fever as observed particularly in patients in the latter half of 1952.

In Korea almost all cases occurred among troops serving in forward areas, the greatest incidence being in those sectors with a heavy growth of grass and brush and infested by a large rodent population. The prevalence of the disease showed a distinct seasonal trend. (Fig. 1.) The spring outbreak in 1952 began about the end of April and reached a peak in early June, declining in July and August. The fall outbreak began in late September and reached its peak in November. Few cases were seen from December to April.

The clinical course of hemorrhagic fever may be arbitrarily divided into four phases, each designated for a characteristic physiologic aberration: (1) febrile, (2) hypotensive, (3) oliguric and (4) diuretic. It should be recognized that there is considerable variation among patients, not only in the incidence of various manifestations of the disease but also in the severity of the individual phases. The criteria by which the severity of the different phases was classified as mild, moderate or severe are indicated in Table I. Almost two-thirds of the 264 patients observed in the fall epidemic had a mild over-all course. Three-fourths of these were mild in all phases of their illness but a few experienced a severe diuretic phase and prolonged convalescence. Fourteen per cent of the patients were considered to have had a severe over-all course, the typical clinical and laboratory manifestations being shown schematically in Figs. 2 and 3. All phases of the disease were severe or moderately severe in most of these patients but an occasional patient would have mild febrile and hypotensive phases only to develop serious complications during the oliguric and diuretic phases.

1. Febrile Phase. Approximately 20 per cent of the patients described vague prodromal symptoms which in general resembled mild upper

* From The Medical Service of the 48th Surgical Hospital (Mobile Army). Presented as part of a Symposium on Hemorrhagic Fever before the 38th Parallel Medical Society, Uijongbu, Korea, April 5, 1953. Requests for reprints should be addressed to Dr. David P. Earle, New York University College of Medicine, New York 16, N. Y.

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respiratory infections or gastrointestinal upsets prior to the development of fever and prostration. However, in the majority of instances the onset was abrupt with chills and fever, lethargy, weakness and sometimes dizziness. Within a few hours the patient was more or less prostrated and began to have marked thirst and anorexia. Nausea and vomiting sometimes occurred at this time but usually developed a few days later. Headache, usually frontal or retro-orbital, frequently occurred early and was occasionally associated with pain on movement of the eyes and photophobia. Generalized aching was also an early complaint. Dull, low lumbar aching, and diffuse, non-localizing abdominal pain were common; in a few instances abdominal pain was so severe as to simulate an acute condition of the abdomen. A few patients presented neck pain and some muscular stiffness suggestive of meningismus.

On physical examination the patients appeared to be acutely ill, with an erythematous flush of the head, neck, shoulders and upper thorax. Blanching occurred on pressure over the erythematous areas and dermographism could be demonstrated. The conjunctivae were injected and on the third to the fifth day some patients developed conjunctival petechiae. Subconjunctival edema was infrequent in the initial phase. Subconjunctival hemorrhage, frequently noted in the past,[3–6] was a rarity in our experience, perhaps because of earlier evacuation of patients to the hospital together with avoidance of excessive fluid intake.[7] Petechiae were also

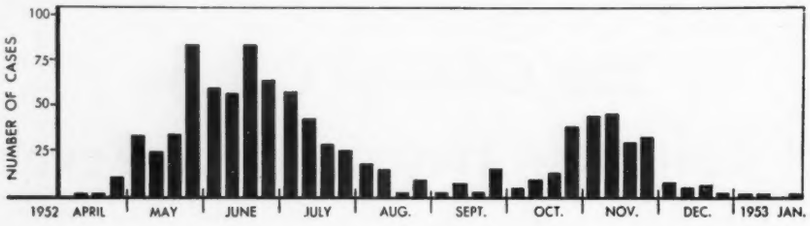

FIG. 1. Seasonal incidence from April, 1952, to January, 1953, during two outbreaks of hemorrhagic fever. Cases seen at the Hemorrhagic Fever Center, Korea.

TABLE I

CRITERIA FOR ESTIMATING SEVERITY OF THE VARIOUS PHASES OF HEMORRHAGIC FEVER

Phase	Observation	Criteria for Severity		
		Mild	Moderate	Severe
Febrile	Max. temperature °F.	100–103	104	105 or more
	Days temp. over 100°C.	1–5	6	7 or more
	Petechiae, flush, injection	0–1+	2–3+	4+
	Max. WBC count	<14,500	14,500–30,000	30,000 or more
Hypotensive	Max. hematocrit	to 50	51–56	57 or more
	Min. systolic B.P.	96–120	81–95	80 or less
	Hours of hypotension	less than 24	24–47	48 or more
	Min. platelets	90,000 or more	40,000–89,000	39,000 or less
Oliguric and diuretic	Min. hematocrit	45 or more	35–44	34 or less
	Max. systolic B.P.	140 or less	141–169	170 or more
	Days of hypertension	less than 1	1–2	2 or more
	Max. BUN	20–79	80–149	150 or more
	Days of proteinuria	to 4	4–5	5 or more
	Max. daily urine vol.	3,400 or less	3,500–4,900	5,000 or more
Convalescence	Days to 12-hour urine concentration test of sp. gr. 1.023	33 or less	34–54	55 or more

seen on the skin, usually in the axillary folds and occasionally over the face, neck and upper thorax. The soft palate was usually diffusely reddened, as were the tonsils, but without sore throat. The presence of a palpable spleen was unusual and was generally attributable to malaria, which coexisted in about 1 per cent of the patients. A moderate generalized lymphadenopathy sometimes was noted about the second day.

The temperature characteristically fluctuated during the day. The day of highest fever occurred earlier in the milder instances of hemorrhagic fever than in the severe cases. In general, the degree of flush, fever and conjunctival injection, as well as the number of petechiae, correlated quite well with the over-all severity of the illness.

Laboratory studies during the febrile phase did not reveal any striking abnormalities. Some patients had a normal or slightly decreased white blood cell count but most developed progressive leukocytosis with an increased number of myeloid elements. Barbero et al.[3] have demonstrated the early presence of myelocytes and metamyelocytes which reach a peak about the seventh day, after which lymphoid elements predominate. Myeloblasts were only rarely seen. In a few instances white blood cell counts of 100–200,000 have been encountered. Blood platelets usually began to decrease in the febrile phase. Eosinophil counts showed prompt and significant fall in all except the severely ill patients.[8] Examination of the urine showed no abnormalities until about the fifth day, at which time proteinuria appeared, usually quite abruptly.

The times of first appearance and of maximum changes, and the usual duration of several important features during the febrile and hypotensive phases of hemorrhagic fever, are shown schematically in Figures 2 and 3. The incidence and usual duration of signs and symptoms are indicated in Fig. 4.

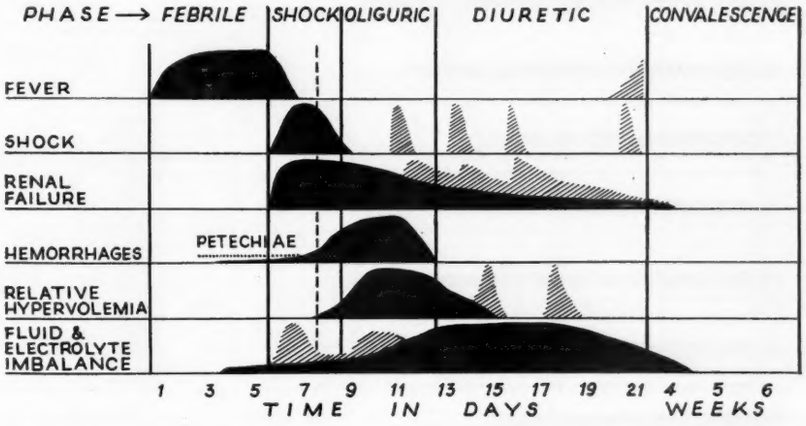

FIG. 2. Course of certain clinical manifestations of severe hemorrhagic fever—schematic.

2. Hypotensive Phase. During the last twenty-four to forty-eight hours of the febrile phase, about the fifth day of illness, hypotension or shock may occur. In the milder instances only a transient fall in pressure was seen which lasted a few hours. Such patients showed only slight decrease in pulse pressure, slight elevation of hematocrit and no significant reduction in platelets. Patients who developed clinical shock exhibited greater changes in these measurements. If high fever was present or persisted during shock, the prognosis was usually poor.

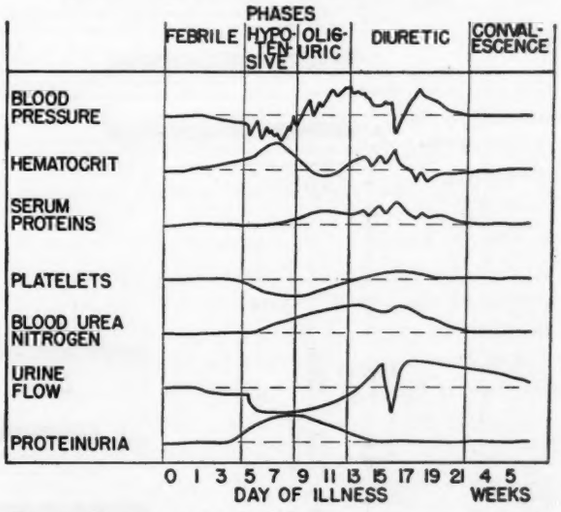

FIG. 3. Course of certain laboratory measurements in severe hemorrhagic fever—schematic.

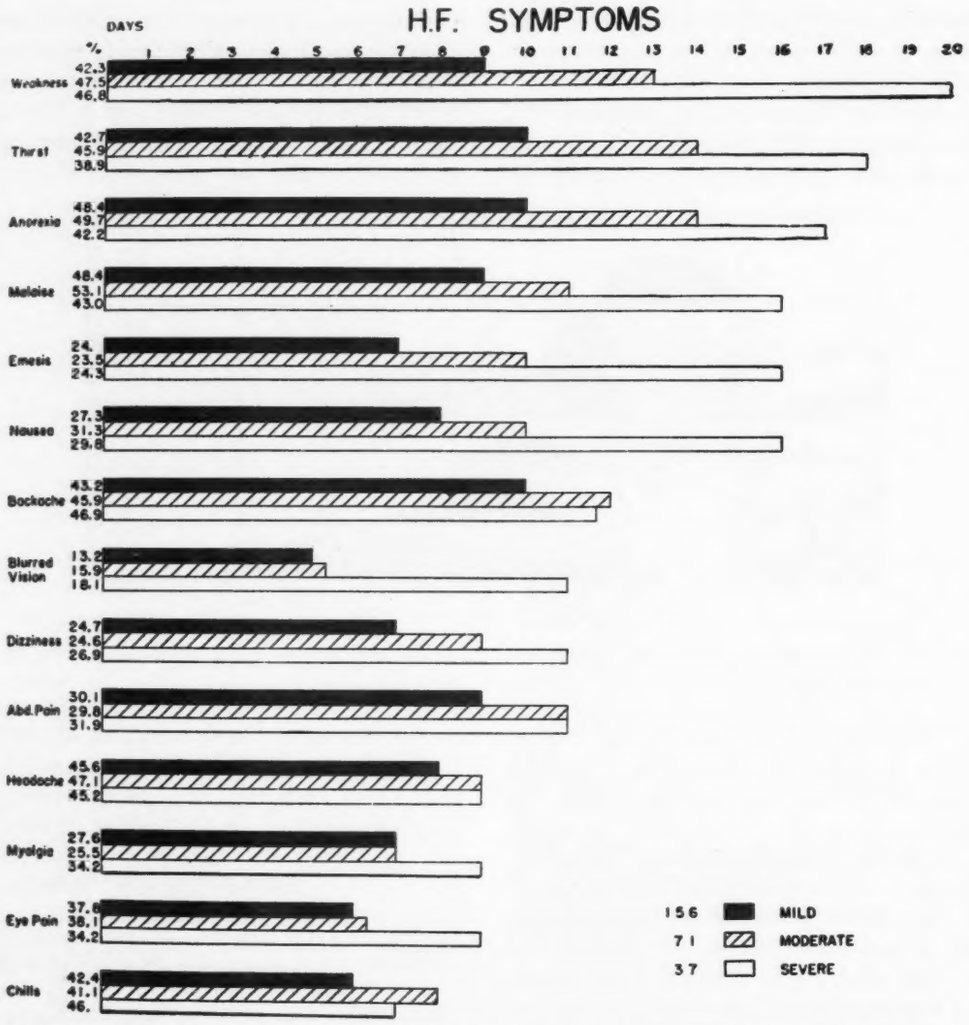

FIG. 4A. Duration and average percentage of the principal symptoms of hemorrhagic fever.

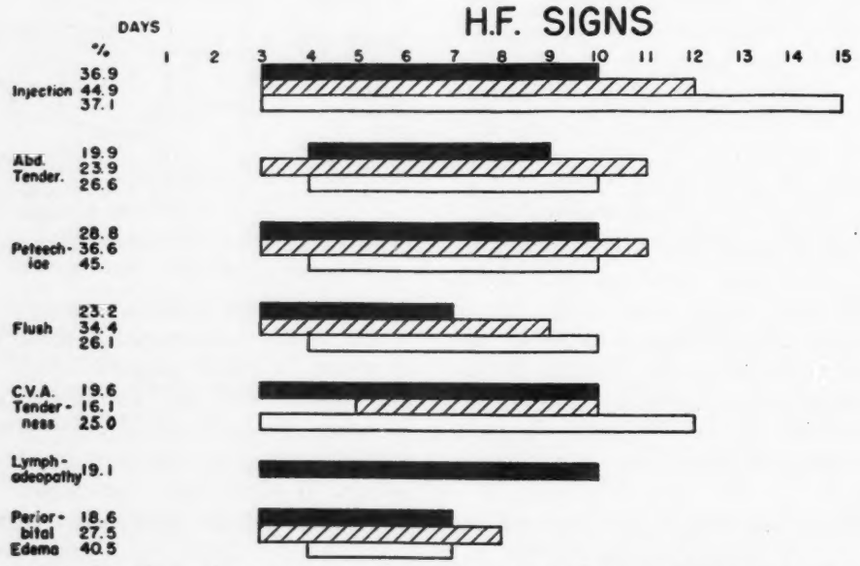

FIG. 4B. Duration and average percentage of the principal signs of hemorrhagic fever.

Among moderately and severely ill patients hypotension or shock began later but persisted for one to three days.

As can be seen in Figures 2 and 4 many of the signs and symptoms present in the febrile phase persisted into the hypotensive and later phases.

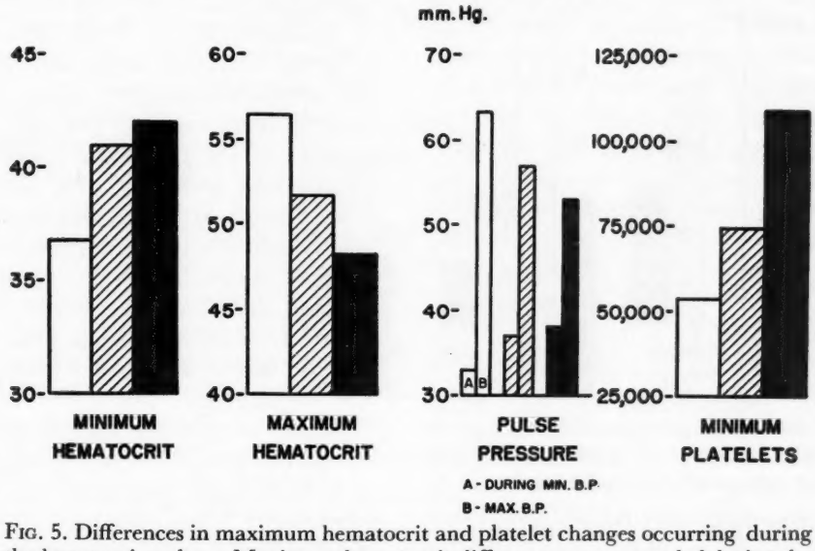

FIG. 5. Differences in maximum hematocrit and platelet changes occurring during the hypotensive phase. Maximum hematocrit differences were recorded during the hypertensive phase. Minimum hematocrit differences were recorded during the hypotensive period. Differences in pulse pressure are shown during the hypo- and hypertensive periods. All findings are depicted in relation to over-all severity of illness. Hollow bars, severe; cross-hatched bars, moderately severe; solid bars, mild.

Symptomatically, myalgia, lumbar backache, anorexia, dizziness and nausea with or without emesis were prominent complaints. Headache diminished but thirst persisted. Some patients were apprehensive, others were very restless or developed confusion, delirium and coma toward the end of this phase. On examination at this time the patient usually presented many or all of the signs seen during the febrile phase. It is particularly noteworthy that most patients had warm, dry skin and extremities in the initial stages of the hypotensive phase. These became cold and moist as the systolic pressure decreased, the pulse pressure narrowed and the shock became more profound. Tachycardia was a valuable sign of shock, for a relative or absolute bradycardia was common in the milder instances of the disease.

At this stage of the disease an increase in hematocrit with no change in the total serum protein level was found,[9] reflecting a loss of plasma through damaged capillaries. This process probably accounts for the edema of the bulbar conjunctivae and the abdominal and lumbar pains.

About the fifth day all patients, irrespective of the degree of severity of the disease, showed a rather rapid onset of marked proteinuria. A patient may have a negative or 1 plus reading in the morning and 4 plus proteinuria that evening. Slight microscopic hematuria was frequently seen. The previously normal specific gravity of the urine began to fall at this time and in two or three days was usually around 1.010. Oliguria now developed and the blood urea nitrogen began to increase. These changes occurred even though shock or hypotension may not have developed.[10,11] Other laboratory studies disclosed an increased white blood cell count, usually with the previously described leukemoid reaction. Blood platelets decreased to minimum values, often below 70,000 per cu. mm., in the more severely ill patients. (Fig. 5.) Clot retraction might be delayed and bleeding time prolonged.

3. Oliguric Phase. As the patient recovered from hypotension the blood pressure often returned to the normal range but in some instances increased to hypertensive levels within a short time. This was associated with a widening of the pulse pressure, a decrease in pulse rate and a return of the hematocrit to normal or low normal values.

Although oliguria may have developed earlier, especially in those who experienced shock, this feature now became prominent in almost all patients. The oliguria appeared to be more or less proportionate to the over-all severity of the disease. The blood urea nitrogen increased rapidly, and electrolyte abnormalities such as hyperkalemia, hyperphosphatemia and hypo-

calcemia often developed in the more severely ill patient. The hypocalcemia was not associated with tetany. Acidosis was rarely severe, for some curious reason.

Symptomatically, the patient continued to be weak, thirsty, have backache and some headache. Nausea and emesis were troublesome in the more severely ill patients. Physical examination of the patient at this time disclosed that many of the previously described signs had disappeared. Although the blood platelets began to increase toward normal, hemorrhagic manifestations such as gross hematuria, and less commonly ecchymoses, subconjunctival hemorrhages, hemoptysis and bleeding from the gastrointestinal tract, now often became more prominent. One patient had an estimated hemorrhage of over 1,500 ml. from the upper gastrointestinal tract. Only a few patients required blood transfusions.

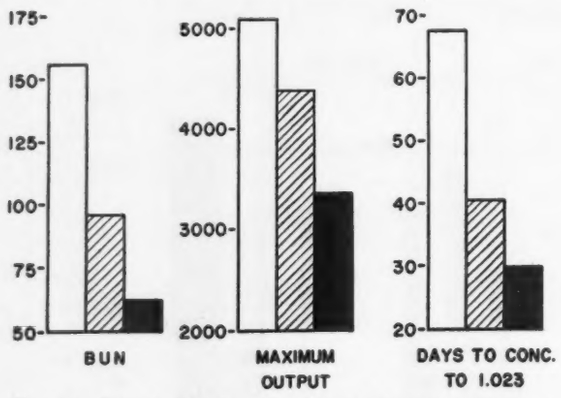

FIG. 6. Principal laboratory data depicting altered renal function, in comparison with over-all severity of illness. Hollow bars, severe cases; cross-hatched bars, moderately severe cases; solid bars, mild cases.

Toward the end of the oliguric phase or with the onset of diuresis about the seventh day in moderately ill patients and the ninth or tenth day in severely ill patients, new symptoms may appear. These are discussed in more detail in another paper of this series[10] but the more important include electrolyte, fluid, central nervous system or pulmonary complications. The central nervous system symptoms may resemble those of the uremic state, with weakness and lethargy, but more often the patient was restless and developed hallucinations, tremors or convulsions. A few instances of transient motor disturbances, usually involving cranial nerves, have been noted. These disturbances seemed to be related more often to the degree of hypertension than to anything else. Application of tourniquets to the extremities or venesection sometimes produced dramatic clearing of the sensorium.[12] Although the peripheral veins might be distended, venous pressures were usually normal at this time[13] and chest roentgenograms rarely revealed any significant cardiomegaly. The pulmonary complications are the most dreaded and of fifteen patients with these, only two survived.[10]

4. Diuretic Phase. With the onset of diuresis, progressive improvement was the rule. During this period of increased urinary output the volume of urine excreted per day varied with the severity of the preceding manifestations of the disease and probably with the severity of the renal lesion. Although the blood urea nitrogen might continue to increase during the first few days of diuresis, it then rapidly returned to normal. Proteinuria generally disappeared with the onset of diuresis. Most patients began to eat well at this juncture and to regain the weight and strength they lost.

However, patients who were severely ill prior to diuresis sometimes continued to be extremely sick and might present a variety of fluid and electrolyte abnormalities.[14] The considerable diuresis in an already dehydrated patient sometimes rapidly produced such a markedly negative fluid balance that shock again supervened. Further, many of the complications which developed in the oliguric phase occasionally continued into or even first arose in the diuretic phase. These included pulmonary and central nervous system manifestations. Finally, anorexia and vomiting might persist unabated.

Convalescence. Except for polyuria and inability to concentrate urine normally, the majority of patients exhibited few if any symptoms or signs during convalescence. By the end of two months most patients could concentrate their urine to a specific gravity of 1.023 or better after a twelve-hour period of water deprivation. (Fig. 6.) None of the patients developed persistent proteinuria.

A few patients who survived an unusually severe attack of hemorrhagic fever had a very prolonged convalescence. Anemia and impaired urinary concentrating ability persisted for more than four months in some of these instances. The only other permanent residua observed to date among these patients resulted from central nervous system hemorrhages.

Mortality. The mortality rate indicated by Russian and Japanese writers and experienced among UN forces in 1951 was about 10 per cent. Perhaps because of earlier evacuation of cases

and improved management this was reduced to about 5 per cent at the Hemorrhagic Fever Center.

ILLUSTRATIVE CASE REPORTS

CASE I. This twenty-two year old white, American soldier was admitted to the Hemorrhagic Fever Center on December 29, 1952. He had been in Korea for five months and had been serving with a Signal Company in a forward area. Previous health had been excellent. His present illness began abruptly on December 24, 1952, with supraorbital headache, eye pain and mild backache. He was seen at his unit dispensary where his throat was noted to be reddened. For this he was given an injection of penicillin. Chills of moderate severity followed during that day and night and on December 26, 1952, he was hospitalized. On admission he was quite weak and complained of chilly sensations, frontal headache, myalgia and thirst. The temperature was 102.8°F. and moderate injection of the pharynx and palate, together with mild conjunctival injection, were noted. The white blood cell count and differential were normal as was the urinalysis except for a 1-plus protein reaction. The patient was treated with aureomycin but continued to have a spiking fever varying from 101° to 102.5°F. On December 28, 1952, the urine contained 3-plus protein and the patient was transferred to the Hemorrhagic Fever Center on the fourth day of illness.

On admission chills and fever were subsiding and slight headache and backache with generalized weakness were the only complaints. Physical examination revealed a moderately ill patient in good nutritional status. No definite flush could be seen in the head and neck region. A few fading petechiae were noted on the axillary folds. No petechiae or injection could be detected in the palate or conjunctivae. Slight enlargement of the posterior cervical nodes was present. The remainder of the examination was not remarkable except that the tip of the spleen was just palpable. The white count was 10,300 per cu. mm. with 71 per cent polymorphonuclear leukocytes of which 19 per cent were band and 2 per cent were juvenile forms. Succeeding counts were within normal limits. Several platelet counts varied from 122,000 to 190,000 per cu. mm. Proteinuria (4-plus) was noted on December 28, 1952 and disappeared on December 31, 1952. Urinary specific gravity on December 26th and 28th was 1.023 in random specimens. On December 30th all specimens showed a specific gravity of 1.005 but no significant formed elements were found. On December 30th the blood urea nitrogen was 39 mg. per cent and receded to 13 mg. per cent on January 5, 1953. Several determinations of serum Na, K, chlorides and CO_2 combining power were all within normal limits. A throat culture shortly after admission showed alpha hemolytic streptococci and N. catarrhalis. A heterophil antibody agglutination test was negative. A chest film was normal.

During the patient's hospital stay the temperature, pulse and blood pressure remained within normal limits. A mild degree of anorexia persisting for three days, in addition to slight myalgia and backache, were the only subjective complaints. On January 8, 1953, a twelve-hour concentration test revealed a maximum urinary specific gravity of 1.010. Urinary output averaged 1,500 ml. until December 30, 1952. After this it increased to an average of 4 L. per day for three days. On January 15th, twenty-two days after onset, the concentrating ability increased to 1.024 and the next day the patient was returned to full duty.

Comment. This patient presents the typical findings and course of a mild case of hemorrhagic fever. No evidence of hypotension or capillary leakage of plasma was noted.

CASE II. This twenty-seven year old white American soldier became ill on October 11, 1952. He had been in Korea ten months serving with a unit in a forward area. The present illness began with sudden onset of chills, fever, frontal headache, backache, anorexia and nausea. In spite of these symptoms the patient continued to perform duty for two days before reporting for sick call. On October 14, 1952 he developed marked weakness and was brought to the dispensary where his temperature was noted to be 105°F. Physical findings disclosed a marked flush of the head and neck together with a reddened throat and injection of the conjunctivae. One injection of penicillin was given and he was evacuated to the Hemorrhagic Fever Center. On admission the complaints were the same and in addition he noted generalized "bone pain" together with blurring of vision. Physical examination disclosed an acutely ill patient in good nutritional status. He appeared rational but was very restless and apprehensive. A mild flush was seen over the head and neck and some petechiae were noted in the axillary folds. The conjunctivae and palate were intensely injected and many

petechiae were seen. The temperature was 104°F., blood pressure 90/78 and pulse 100. The remainder of the examination was normal.

On the sixth day of illness the white blood cell count was 41,000 per cu. mm. with a leukemoid type of differential. Urinalysis revealed a specific gravity of 1.033 with a 4-plus proteinuria. A few erythrocytes were seen microscopically. The blood urea nitrogen was 35 mg. per cent, the hematocrit was 51 and the erythrocyte sedimentation rate 4 mm./hr. Serum creatinine, CO_2 combining power, sodium, potassium and chlorides were within normal limits. A chest film was normal.

The patient was placed in Trendelenburg position for one hour during which time the systolic pressure remained at about 89 mm. Hg. A continuous intravenous infusion of L-arterenol (40 μg. per ml. per minute) was begun. This maintained blood pressure for twelve hours but then the pulse pressure narrowed and finally the blood pressure became unobtainable. After three units of concentrated human salt-poor serum albumin had been given the pulse pressure widened and normotensive pressure was restored. During the next two days the patient continued to have a fever of 104°F. and increased hematocrit, and required L-arterenol in an average dosage of 20-μg. per minute to maintain blood pressure. At the end of this time the patient suddenly became restless and cyanotic and his blood pressure was again unobtainable. Supplies of L-arterenol were now exhausted and neosynephrine was substituted. Serum albumin was again administered. After thirty minutes 20 units of pitressin were given but the blood pressure was still unobtainable. The hematocrit was decreasing, and after a transfusion of 500 ml. blood the blood pressure slowly returned to normotensive levels. The heart rate was 120 and a gallop rhythm could be heard during this episode. The urine output on this day was 390 ml. with an intake of 3,360 ml. The blood urea nitrogen increased to 78 mg. per cent. The urine had a specific gravity of 1.022 with 4-plus protein. The next day the sensorium cleared and the blood pressure was more stable. The neosynephrine infusion had gradually been reduced to 3 μg. per minute. The site of a previous arterial puncture was now noted to be oozing and a large hematoma had formed. The bleeding time was three minutes, clotting time twenty minutes (Lee-White), clot retraction poor and the prothrombin time 50 per cent of normal. The blood platelets were 28,000 per cu. mm. A blood volume determination (T-1824 method) showed a reduction to 30 per cent below normal. The hematocrit decreased to 26. By the end of the day another fresh whole blood transfusion (500 ml.) was given. After this no further bleeding from the arterial puncture site occurred. Also at this time the patient began having a troublesome cough, productive of purulent, blood-streaked sputum for which aureomycin therapy was begun.

On the following day (twelfth day of illness) the patient slowly improved and became afebrile. However, anorexia, nausea and occasional emesis continued. His blood pressure remained at normotensive levels and neosynephrine was discontinued. The bleeding and clotting abnormalities had returned to normal save for some lowering of the platelets and slight prolongation in prothrombin time.

The patient had in the meantime become progressively more oliguric, with an output of about 100 ml. urine per day. The blood urea nitrogen had risen to 182 mg. per cent. During the next few days aureomycin was continued and the sputum gradually decreased in amount. Because of the marked oliguria and rapidly increasing azotemia, the patient was transferred on the fifteenth day of illness to the 11th Evacuation Hospital where hemodialysis could be carried out if hyperkalemia should become a serious problem. There were no additional complaints and most of the previously noted symptoms were subsiding except for continued anorexia, nausea and intermittent emesis. No remarkable physical findings were present other than obvious wasting. Aureomycin was discontinued. The blood pressure had risen to 150/90. An electrocardiogram showed some peaking of the T waves. The serum potassium was 5.0, sodium 133 and chlorides 102 mEq./L. The CO_2 combining power was 21 volumes per cent. To prevent further hyperkalemia 60 gm. of K-exchange resin (SKF-648) was given daily as an enema and thereafter the serum potassium never rose above 6 mEq./L. Epistaxis occurred several times but no other hemorrhagic manifestations were noted.

Diuresis began on the seventeenth day of illness and increased progressively to a maximum of 6 L. per day. At this time the blood pressure was 170/90, the hematocrit was 27, serum NPN 427 mg. per cent, CO_2 combining power 27 volumes per cent and chlorides 77 mEq./L.

Urinalysis revealed a specific gravity of 1.010 with 2-plus proteinuria. Several grand mal type convulsions occurred during the next seven days, together with emesis of about 2 to 3 L. per day.

As diuresis continued the patient slowly improved, all symptoms subsiding by the twenty-second day. Oral intake of food slowly increased and he regained strength. The electrocardiographic and clotting abnormalities returned to normal. Several days later the patient developed a purulent conjunctivitis which responded to terramycin ophthalmic ointment. Pain and tenderness were noted in the right calf, along the course of the saphenous vein, presumably the result of the continuous intravenous pressor therapy. This cleared without anticoagulant therapy.

On the thirty-ninth day of illness the patient was improving rapidly and was transferred back to the Hemorrhagic Fever Center for the remainder of his convalescence. On readmission he was asymptomatic and had no remarkable findings aside from obvious wasting. During the next month the patient slowly regained weight and strength. Ferrous sulfate was given for his anemia with a slow but progressive response. The urinary specific gravity slowly improved and reached a maximum of 1.012 on the sixty-fifth day of disease. Because of the marked severity of this patient's illness and the need for prolonged convalescence, the patient was returned to the United States for further follow-up.

Comment. This patient depicts the findings and course of a severely ill patient with hemorrhagic fever. The high fever for twelve days was unusual. Severe and prolonged shock required the use of large amounts of vasoconstrictors and serum albumin. The need for transfusions was unusual. In the oliguric phase, which was profound and prolonged, marked azotemia, epistaxis and central nervous system signs, together with hypertension, illustrate the classical manifestations of the more severely ill patient. The marked diuresis and prolonged abnormality in urinary concentrating ability indicated a marked degree of renal damage.

DISCUSSION

The diagnosis of epidemic hemorrhagic fever should be entertained when a person who has recently been in an endemic area complains of sudden onset of chills, fever, prostration, frontal headache, marked thirst and myalgia (particularly ache in the low lumbar region), and on physical examination exhibits a marked facial flush, injection of the palate and conjunctivae, and petechiae of the conjunctivae, palate, axillary folds and waist line. The presence of proteinuria and reduction in the specific gravity of the urine, together with azotemia, will confirm the diagnosis when other renal diseases have been excluded. While these symptoms and signs are in no way specific, the clinical picture, when full-blown, is quite distinctive. In the early phases, however, diagnosis may be difficult, particularly in respect to differentiation from infections of the upper and lower respiratory tract. Cases which eventually proved to be virus hepatitis, infectious mononucleosis, malaria, relapsing fever, rheumatic fever and leptospirosis occasionally were admitted to the Hospital as suspected hemorrhagic fever. Meningitis and encephalitis were not common but were confusing since a few cases of hemorrhagic fever, all severely ill, were noted initially to have meningismus, disorientation and equivocal reflex changes. Gastroenteritis, usually due to Salmonella infection, ordinarily presented no diagnostic problem. Of particular importance is the exclusion of other types of renal disease, such as pyelonephritis and glomerulonephritis. Three cases were encountered during the period of this study which were believed to represent exacerbations in chronic glomerulonephritis rather than hemorrhagic fever.

A large number of patients were seen who had a mild febrile illness without localizing signs or symptoms. Blood, urine and stool cultures, routine laboratory studies and multiple agglutination tests were negative. The patients improved rapidly and were discharged with the diagnosis of "fever of undetermined origin." Some of these patients may indeed have had unrecognized mild hemorrhagic fever.

The abrupt onset of hemorrhagic fever is similar to that seen in many acute febrile illnesses. It might be inferred that this represents the period of invasion by the causative agent. The generalized manifestations without early specific localization suggests wide dissemination. The development of hypotension or shock recalls the fact, well known to physicians who practiced in the pre-antibiotic era, that severe febrile illnesses such as typhoid fever and lobar pneumonia were sometimes characterized by hypotension or shock at the time of defervescence. This phenomenon has also been described during

the course of Rocky Mountain spotted fever and typhus and in elderly patients with severe pneumonia.[15] Vasodilatation has been considered to be the principal physiologic disturbance responsible for the hypotension seen in these situations. A similar phenomenon may contribute to the hypotension of hemorrhagic fever[12] but, in addition, circulating blood volume is reduced through loss of plasma by way of damaged capillaries.[17] The possibility that such loss of plasma through the capillaries or that shock might be related to failure of the pituitary-adrenal axis has been considered. Thorn and associates[17] have noted diminished sensitivity to L-arterenol in adrenalectomized animals and a summation of effect when this agent is given with corticosteroids. Studies on ketosteroid and corticoid excretion in hemorrhagic fever[18] indicate adequate response in the mildly and moderately ill patients, but in the severely stricken group a marked reduction was noted. Whether or not this indicates a state of adrenal exhaustion is uncertain, since renal function was grossly impaired at this time.

SUMMARY

1. The clinical characteristics and course of epidemic hemorrhagic fever are described on the basis of observations made on United Nations forces hospitalized at the Hemorrhagic Fever Center in Korea in 1952.

2. The clinical picture is characterized by sudden onset, in a person recently situated in an endemic area, of chills, fever, prostration, frontal headache, marked thirst and myalgias. There is a marked facial flush, injection of the palate and conjunctivae, and petechiae of the conjunctivae, palate, axillary folds and waist line. Proteinuria and reduction in specific gravity of the urine are present.

3. The clinical course may be divided into four phases, each designated for a characteristic physiologic aberration: (1) febrile, (2) hypotensive, (3) oliguric and (4) diuretic. The presenting clinical features of each phase are described.

4. Two representative case histories, one illustrating a mild course and the other a severe attack, are summarized.

5. The differential diagnosis is briefly considered.

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The Sequelae of Epidemic Hemorrhagic Fever*

With a Note on Causes of Death

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THE many and varied manifestations of hemorrhagic fever have been described both in this symposium and elsewhere.[1–6] Several analyses of the pathology of the disease, including comments on the causes of death, are also available.[7–9] However, detailed information on some of the features and their inter-relations has not been extensive or was based on a limited number of patients. The purposes of the present paper are to present an analysis, from a largely clinical point of view, of the causes of death in hemorrhagic fever, and to present data on several important features and complications that contribute either to the severity or to the mortality of the disease.

CLINICAL MATERIAL

The data presented in this paper are based upon observations of 828 patients with hemorrhagic fever treated at the Hemorrhagic Fever Hospital in Korea during the last nine months of 1952. Of the 828 cases‡ observed, 479, or 58 per cent, had one or more of the manifestations or complications listed in Table 1 and discussed in the following sections. Forty-two per cent had none of these features. All patients, however, had proteinuria and other more minor features of the disease, while the vast majority had some degree of renal failure. Hence, although very important, renal failure is not included in the list of manifestations.

TABLE 1
COMPLICATIONS IN 828 CASES OF HEMORRHAGIC FEVER*

	No. of Patients	Per cent
Hypertension	208	25
Shock	137	16
Hypotension without shock	118	14
Hemorrhages	90	11
Electrolyte abnormalities	89	11
Central nervous system complications	87	11
Anemia	61	7
Pulmonary complications	53	6

* Renal complications were present in all instances but are not included in this classification for reasons stated in the text.

HYPOTENSION AND SHOCK

Decrease in arterial blood pressure at the time of defervescence in hemorrhagic fever may vary from mild hypotension to fatal shock. Comparison of patients with clinical shock with those who had mild hypotension but no shock were

‡ This analysis of complications is based on fewer patients than in the companion analysis of the clinical course.[6] The patients in the present study were limited to those admitted in 1952 whereas the clinical study included patients admitted during the first few months of 1953 as well.

* From the Medical Service of the 48th Surgical Hospital (Mobile Army), APO 301. A portion of this paper was presented as part of a symposium on Epidemic Hemorrhagic Fever before the 38th Parallel Medical Society, Uijongbu, Korea, April 5, 1953. Requests for reprints should be addressed to Dr. David P. Earle, New York University College of Medicine, New York 16, N. Y.

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made to elicit, if possible, any differences in their clinical courses prior and subsequent to the change in blood pressure.

All of the patients considered to be in shock had several or all of the following manifestations: lowering of the systolic and frequently of the diastolic blood pressure, weak radial artery pulsations, tachycardia and prolonged blanching time of the skin. Warm, dry skin was usually seen initially, the skin later becoming cold and moist in protracted or terminal shock, especially if treated with pressor drugs.

One hundred thirty-seven (16.5 per cent) of the 828 patients had clinical shock, while 118 patients (14 per cent) had hypotension without shock. A decrease in systolic pressure of at least 10 mm. Hg to a level below 100 for a minimum of two hours was required for inclusion in the latter group. Although these patients were closely observed for the development of shock, none included in this group exhibited the features of clinical shock just described. Hypotension or shock generally developed between the third and eighth day of illness, with an obvious peak in incidence on the fifth day. Several of the seriously ill patients had a second episode of shock in the later phases of their disease, generally due to fluid and electrolyte disturbances or to severe pulmonary infection.

As the decrease in blood pressure usually occurred at the time of defervescence, it is possible that both changes resulted from cutaneous vasodilatation, a hypothesis which has been entertained for many years as the cause of shock during the crisis of lobar pneumonia.[10] However, an analysis of the rate of fall in body temperature during the twelve-hour period preceding the decrease in blood pressure in patients selected at random showed no difference between those with shock and those with uncomplicated hypotension.

The relation of fluid balance to blood pressure change was also considered. The average daily fluid balance (not including the insensible loss) prior to the blood pressure change was determined for each group. No significant difference in fluid balance was noted in those having only hypotension as compared with those in clinical shock. In addition, an average daily weight loss of 2.4 and 3.4 pounds per day for the shock and hypotensive groups, respectively, indicated that a large insensible fluid loss occurred among patients of both groups. It would seem from these observations that a negative fluid balance was relatively unimportant in the genesis of early shock in hemorrhagic fever.

Leakage of plasma out of damaged capillaries and resultant decrease in circulating blood volume has been proposed as the more important cause of primary shock in hemorrhagic fever.[11]

TABLE II

EXAMPLES OF SEVERE CAPILLARY LEAKAGE ASSOCIATED WITH NO CLINICAL SHOCK AND RELATIVELY MILD SUBSEQUENT RENAL FAILURE

Patient	Hypotensive Phase		Renal Failure		
				Hypertension	
	Maximum Hematocrit	Minimum Blood Pressure	Maximum Blood Urea Nitrogen	Maximum Blood Pressure	Duration (days)
N. E. L.	62	124/76	26	132/72	?
N. E. W.	58	110/70	93	170/120	2
T. D.	58	100/68	97	160/106	4
C. R.	57	107/66	45	162/108	1
P. A.	57	108/80	52	140/88	?
B. L.	57	102/72	77	140/98	1
F. R.	56	102/70	19	134/98	1
D. H.	56	80/40	38	?	?
M. O.	56	104/54	68	136/88	?
M. A.	56	100/68	96	140/88	?

A considerable increase in hematocrit without a corresponding change in total serum proteins during the hypotensive phase is evidence for this phenomenon.[12] The average increase in hematocrit during the twenty-four hours prior to the blood pressure decrease was only slightly greater in the shock group than in those with hypotension only. The most significant difference between the two groups, however, was the further hematocrit increase achieved after the decline in blood pressure had occurred, being three times greater for the shock group. Assuming that proteinuria is another manifestation of increased capillary premeability, it is interesting to note that protein appeared in the urine slightly before the onset of shock but simultaneously with the onset of hypotension without shock. Thus the evidence indicates that plasma leakage occurred in both groups to an equal degree prior to the blood pressure changes, but that after the initial pressure change, loss of plasma was greatly accelerated in those in whom

a profound blood pressure decrease and clinical shock developed.

Of 193 patients who had frequent hematocrit determinations, forty-five exhibited maximum readings of 55 or more. In thirty-three of these clinical shock developed. However, marked loss of circulating plasma volume as reflected by a considerable increase in the hematocrit is not necessarily associated with shock or serious renal failure. Data from several selected patients to illustrate this point are given in Table II.

Nevertheless, most of the mortality in hemorrhagic fever occurred among patients who had had significant shock at some time prior to death. Thus 32 per cent of the 137 patients who had had clinical shock either died in shock or subsequently of other complications. None of the 118 patients who were classified as hypotensive without shock died, while only three of the 573 patients who did not have any decrease in blood pressure died. As a group, in those patients with shock a more severe degree of renal failure developed (mean blood urea nitrogen 148 mg. per cent) than in those with simple hypotension (84 mg. per cent). Despite these general correlations there were many exceptions, as illustrated in Table III which presents data from a few selected patients in whom there was little or no hypotension or hematocrit increase and yet severe renal failure developed. An analysis of the maximum hematocrit during the hypotensive phase and the maximum blood urea nitrogen level during renal failure (Table IV) reveals some degree of correlation between these features but also indicates that there are obvious exceptions to the general rule.

TABLE III

EXAMPLES OF MILD HYPOTENSIVE PHASE FOLLOWED BY SEVERE RENAL IMPAIRMENT

(In All Patients 3 to 4 Plus Proteinuria Developed)

Patient	Hypotensive Phase				Evidence of Renal Function Impairment						
	Maximum Hematocrit	Minimum Blood Pressure	Hours Blood Pressure <110/60	Maximum Pulse	Maximum Blood Pressure	Days Blood Pressure >140/90	Maximum Blood Urea Nitrogen (mg. %)	Minimum Daily Urine (ml.)	Days Urine <500 (ml.)	Maximum Daily Diuresis (ml.)	Days Specific Gravity* <1.015
T. U.	46	122/90	0	86	170/115	7	118	190	1	3000	18
G. O.	48	126/90	0	92	162/102	5	125	420	2	3500	23
S. T.	48	106/62	3	88	152/94	4	162	140	2	5400	21
B. E.	49	118/84	0	88	170/114	8	105	160	4	5300	27
C. O.	49	110/70	0	76	138/92	0	105	570	0	4900	3
S. A.	49	106/52	12	84	142/100	2	103	0	2	2600	21
B. R.	49	100/60	4	96	140/98	1	100	180	2	2900	15
R. U.	50	108/60	4	88	164/120	6	143	510	0	5100	17

* Maximum specific gravity of urine after twelve-hour concentration test.

HEMORRHAGIC MANIFESTATIONS

Hemorrhagic manifestations were impressive enough to lead early investigators to name the disease after this feature. However, this designation overemphasizes the incidence of serious hemorrhagic complications. Excluding petechiae which are common during the late febrile and hypotensive phases and which are usually associated with increased capillary fragility, other obvious hemorrhages occurred in only

TABLE IV

RELATION BETWEEN MAXIMUM BLOOD UREA NITROGEN AND MAXIMUM HEMATOCRIT IN EIGHTY-NINE CASES OF EPIDEMIC HEMORRHAGIC FEVER

Maximum Hematocrit	No. in Group	Maximum Blood Urea Nitrogen (mg. %)	
		Mode	Range
<49	25	60	11–144
50–59	58	95	15–204
>60	6	185	116–210

ninety of the 828 patients. In forty-seven of these the hemorrhagic manifestations included relatively minor features such as epistaxis, ecchymoses or subconjunctival hemorrhages. More important manifestations were hematemesis, melena, hemoptysis and gross hematuria but even these rarely caused any real concern, blood transfusions being required in only a handful of patients. Hemorrhages into the central nervous system, however, could produce serious or fatal results.

Although thrombocytopenia is common and at its maximum during the hypotensive phase,[1,5,13] the correlation between blood platelets and the degree of shock, the maximum hematocrit and the incidence of moderate to severe (gross) hematuria is far from precise. Moderate to severe hematuria, however, did appear to be related to the degree of hemorrhage into the renal pelvis or ureter as described in the autopsy protocols of the thirty-nine fatal cases in whom examination of the urine was possible with reasonable frequency. In no instance did moderately severe or gross hematuria occur among patients who died before the onset of diuresis unless considerable hemorrhage into the renal pelvis was present. The converse, however, did not hold since even marked hemorrhage into the renal pelvis could occur with no apparent hematuria. Four of the nine patients who died in the diuretic phase had had severe or gross hematuria during the early oliguric period but at autopsy had only mild or no renal pelvis hemorrhage. It is possible, however, that these patients survived long enough for the pelvic hemorrhage to be reabsorbed or greatly modified.

HYPERTENSION

Hypertension (systolic pressure in excess of 150 mm. Hg, diastolic pressure in excess of 100 mm. Hg) was encountered in 208 (25 per cent) of the 828 patients. The onset of hypertension occurred during oliguria or in the first few days of diuresis in the majority of instances. The mean duration of hypertension was four and a half days, with a range of one to thirty-two days. Persistent hypertension developed in none.

During the fall 1952 outbreak, frequent measurements of both blood pressure and hematocrit were made in 120 patients. Some degree of correlation was found between the incidence of hypertension and the severity of the preceding capillary leakage as judged by the maximum hematocrit during the hypotensive phase. (Table v.) A somewhat better correlation was noted between the incidence of hypertension and the severity of renal failure as reflected by the maximum blood urea nitrogen level. (Table vi.) However, it is again obvious that these relationships are not precise and it would appear that a number of factors condition the development of hypertension in hemorrhagic fever.

TABLE V
INCIDENCE OF HYPERTENSION PERSISTING FOR MORE THAN TWENTY-FOUR HOURS IN RELATION TO MAXIMUM HEMATOCRIT DURING HYPOTENSIVE PHASE

Maximum Hematocrit	No. in Group	No. with Hypertension	Per cent with Hypertension
<49	35	11	32
50–59	77	33	43
>60	8	6	75
Total	120	50	

TABLE VI
INCIDENCE OF HYPERTENSION PERSISTING FOR MORE THAN TWENTY-FOUR HOURS IN RELATION TO MAXIMUM BLOOD UREA NITROGEN

Blood Urea Nitrogen (mg. %)	No. in Group	No. with Hypertension	Per cent with Hypertension
<30	24	0	0
30–60	19	3	18
60–90	30	7	23
90–120	24	13	54
>120	38	26	68
Total	135	49	

ELECTROLYTE ABNORMALITIES

Fluid and electrolyte abnormalities are discussed elsewhere in this symposium.[14] Suffice it to state here that serum sodium levels were less than 130 mEq./L. in fifty-four and exceeded 160 mEq./L. in eleven patients. Serum potassium levels greater than 6 mEq./L. were observed in thirty-seven patients and levels less than 3.5 mEq./L. in eight. A total of eighty-nine patients had one or more of these abnormalities. Relevant data were not obtained during the hospitalization of the first 200 of the 828

patients and serum electrolytes were not measured subsequently in many of the mildly ill patients; the available data therefore do not reflect the true incidence of these abnormalities.

PULMONARY COMPLICATIONS

Pulmonary complications were observed on clinical examination in only fifty-three (6 per cent) of the 828 patients but were of great interest because of their prominence among the causes of death, being second only to shock in that respect. The majority of pulmonary complications occurred during the oliguric and diuretic phases. Wheezes and rhonchi were noted in twenty-two patients. The significance of this finding is not known. Pulmonary edema developed in fifteen patients, thirteen of whom either died in acute pulmonary edema or subsequently of other complications, usually pulmonary infections.

The average daily fluid balance prior to the development of pulmonary edema was calculated for each patient. This varied from a negative balance of 727 ml. to a positive balance of 1,000 ml. per day, neglecting insensible loss. If a minimum insensible loss of 800 ml. per day is assumed, nearly all of the patients were in negative fluid balance. Thus it appears that prolonged overhydration was not the cause of pulmonary edema. Moreover, most of these patients appeared quite dehydrated. Rapid infusion of either large volumes of isotonic solutions or of smaller volumes of hypertonic solutions may have played a role in the genesis of pulmonary edema in these patients since eleven had received some form of intravenous therapy within twelve hours of the onset of their pulmonary edema. While the association of parenteral fluids and pulmonary edema seemed to be coincidental in most of these individuals, in a few the relationship suggested cause and effect.

Swift[4] mentions two cases of hemorrhagic fever with pulmonary edema "with elevated venous pressures, and slight ankle and sacral edema, indicating right heart failure as well." None of the patients with pulmonary edema in the present series had detectable edema elsewhere. Indeed, the retroperitoneal edema so characteristically found at postmortem examination in patients dying in the hypotensive phase was never observed in patients dying with pulmonary edema during the oliguric and diuretic phases. Venous pressure was measured in three patients at the onset of pulmonary edema and was found to be within normal limits. Furthermore, no increase in cardiac size occurred in eight patients in whom x-ray studies were made prior to and during pulmonary edema, and digitalization had no observable effect on the pulmonary edema. Finally, the character of the sputum produced by these patients is worthy of comment for in many cases large amounts of hemogeneous bright red mucoid sputum were produced, distinctly different from the pink, frothy sputum seen in pulmonary edema due to congestive failure. At autopsy many of these patients were found to have focal intra-alveolar hemorrhages.

These observations suggest that the following train of events may take place: An internal fluid shift, perhaps the result of resorption of retroperitoneal edema fluid, may overload the vascular compartment. The pulmonary vascular bed may already have been damaged by the etiologic agent or by other unknown factors which are part of the "uremic" state, making it more susceptible to damage from pressure and volume changes. In any event, the net result seems to be increased pulmonary capillary permeability. Heart failure and extrinsic fluid balance did not seem to play a prominent part in the development of pulmonary edema in the patients who came under our observation.

Pneumonitis was diagnosed when a patient exhibited a recurrence of fever, developed a productive cough and was found to have rales over a localized area of the chest with x-ray evidence of patchy pneumonia. Pneumonia was diagnosed in six patients, while lung abscesses were demonstrated radiographically in two additional patients. At necropsy lung abscesses were found in these two patients as well as in three others. Pneumonitis and focal intra-alveolar hemorrhages were also found at autopsy in some instances when not diagnosed during life.

Two patients who had subcutaneous emphysema of the neck and anterior thorax had no clinical evidence of pulmonary disease but one was later found at autopsy to have severe ulcerative tracheobronchitis.

CENTRAL NERVOUS SYSTEM COMPLICATIONS

Central nervous system symptoms occurred in eighty-seven (11 per cent) of the 828 patients. Disorientation, extreme restlessness, or lethargy were present in forty patients. Paranoid delusions, visual and auditory hallucinations, manic-

depressive states and schizoid reactions occurred in fourteen. Motor or kinetic disturbances as manifested by reflex changes, clonus, tremors, dysarthria, dysphagia and strabismus were present in fourteen patients. Grand mal convulsions occurred in twenty-six patients.

Nearly all the seizures occurred during the late oliguric and early diuretic phases. The blood pressure of patients just prior to seizures was on the average higher than during any of the other central nervous system complications, whereas there appeared to be no correlation between any of these phenomena and hematocrit values, fluid balance and serum calcium, sodium or potassium levels. The mean of the blood urea nitrogen values for the patients at the time of the seizures was 146 mg. per cent with a range of 42 to 220 mg. per cent. Spinal fluid total protein was found to be 80, 82, 68 and 36 mg. per cent in four of these patients. The spinal fluid cell counts, sugar and chloride values were normal.

Although it was believed that only two of the deaths were primarily due to central nervous system involvement, the findings at autopsy suggest that the central nervous system shares in the vascular abnormalities of hemorrhagic fever. These findings include cerebral edema and small subarachnoid, epidural and focal brain stem hemorrhages. Small cerebral abscesses were found in a patient who died with overwhelming pneumonia and multiple lung abscesses.

Late neuropsychiatric abnormalities were not found among a group of thirty convalescing patients, of all degrees of severity, selected at random from the 828 patients.[15] Only one patient, not included in this small series, exhibited a residual psychosis of a paranoid-schizophrenic type which was still present five months after the onset of his illness. No neurologic residua were noted, in contrast to the findings of Powell[16] who observed focal cord damage in a few survivors of his series.

ANEMIA

Using a hematocrit level below 40 per cent as a criterion, anemia was found in sixty-one (7 per cent) of the 828 patients. The onset was almost entirely in the late oliguric and diuretic phases. The duration of anemia was twenty days or less in 49 per cent, twenty-one to forty days in 32 per cent and forty-one days or longer in 19 per cent of the patients.

It is theoretically possible that the large changes in hematocrit (high values during the shock phase and low values during the convalescent phases of the disease) could be due to changes in red cell size. Cell indices were calculated serially throughout the disease in eleven patients who demonstrated such hematocrit changes. No change in cell size could be detected. Although the anemia is usually normochromic and normocytic, macrocytosis has been noted in a few cases. The anemia was not associated with conspicuous reticulocytosis. The mean highest reticulocyte count was 2.4 per cent in these eleven patients. The severity of the anemia appeared to be proportional to the degree of uremia and did not appear to be related to blood loss.

MISCELLANEOUS COMPLICATIONS

Malaria was present in nine patients. Phlebitis occurred secondary to constant intravenous pressor drug infusions in five patients. Genitourinary infections in another five patients were secondary to catheterization. The three instances of gastrointestinal tract obstruction were due to a pyloric ulcer or to impacted ion exchange resins in the sigmoid colon. A single case of ulcerative colitis made its appearance during the diuretic phase of a severely ill patient.

RESIDUA OF HEMORRHAGIC FEVER

Of the 783 patients with hemorrhagic fever who survived, only sixteen were unable to return to duty within a period of four months. Fifteen of these were unable to concentrate urine above a specific gravity of 1.018 and still had polyuria and nocturia four months after the onset of their illness. Anemia was present in nine of these sixteen patients, while one each still had phlebitis, ulcerative colitis and psychosis.

CAUSES OF DEATH*

The causes of death were analyzed in forty-two fatalities that occurred between April and December, 1952, at the Hemorrhagic Fever Hospital. The records of four patients who died during this period were not available. The forty-six fatalities occurred among a total of 828 patients, a mortality rate of 5.5 per cent.

A summary of the causes of death and contributory factors in relation to phase of disease is given in Table VII, while the data for individ-

* This analysis was made by Yoe, R. H., Cugell, D. W. and Earle, D. P.

ual patients are recorded in Table VIII. This analysis is based on a review of the clinical records and on several features recorded in the autopsy protocols including retroperitoneal edema, extent of pulmonary edema, hemorrhage and infection, and extent and location of central nervous system involvement. In some instances it was difficult or impossible to determine which of several processes played the major role in causing death.

The majority of patients had considerable renal failure and nitrogen retention (Table VIII) at the time of death. Renal failure of this degree obviously contributed to the mortality of hemorrhagic fever and was responsible for the development of many of the subsequent serious manifestations. It was so common, however, that it is not included in this analysis.

Shock was a common cause of death. Twelve patients died in early primary shock at or near the time of maximum plasma leakage as evidenced by the hematocrit increase and the presence of extensive retroperitoneal edema. Seven patients died of shock in the transition phase, i.e., as the hematocrit was decreasing and the edema was being absorbed. All of these had had some degree of primary shock but in three this had not been severe. Hyperpyrexia

TABLE VII

SUMMARY OF CAUSES OF DEATH, CONTRIBUTORY FACTORS AND PRIOR EVENTS IN FORTY-TWO FATALITIES DUE TO EPIDEMIC HEMORRHAGIC FEVER *

Phase	No. of Patients	Major Causes of Death	Contributory Factors	Prior Events
Hypotensive	12	11 Primary shock 1 Primary shock and aspiration of vomitus	1 Hyperpyrexia 1 Central nervous system involvement	
Transition	7	3 Transition shock 2 Transition shock and hyperpyrexia 1 Transition shock and hyperkalemia 1 Transition shock and aspiration of vomitus	2 Dehydration 1 Hypernatremia 1 Pulmonary infection	7 Primary shock (6 severe)
Oliguric	10	2 Secondary shock and hyperpyrexia 1 Secondary shock and dehydration 1 Secondary shock, dehydration, potassium deficiency, pulmonary infection and edema 2 Pulmonary infection 1 Pulmonary edema and hypervolemia 1 Convulsion and hypervolemia 1 Dehydration and potassium deficiency 1 Aspiration of vomitus	5 Pulmonary infection 4 Dehydration 1 Hyperkalemia 1 Potassium deficiency 2 Pulmonary edema 1 Hypertension 1 Central nervous system involvement	9 Primary shock (4 severe) 1 Transition shock (moderate) 7 Hypertension
Diuretic	13	1 Secondary shock and dehydration 6 Secondary shock, dehydration, potassium deficiency and pulmonary infection (1 with central nervous system involvement) 2 Pulmonary edema and hypervolemia 1 Potassium deficiency 1 Potassium deficiency and dehydration 1 Potassium deficiency, dehydration and pulmonary infection 1 Pulmonary infection and central nervous system involvement	5 Hypernatremia 4 Pulmonary edema 1 Pulmonary infection 2 Hypertension 2 Central nervous system involvement	11 Primary shock (9 severe) 1 Transition shock (severe) 1 Secondary shock (severe) 3 Hyperkalemia 3 Hypervolemia 8 Hypertension

* Only those factors believed to have played an important role in the fatal outcome are recorded. For example, hyperkalemia is specifically noted only when associated with marked EKG changes although minor degrees of hyperkalemia were commonly observed.

TABLE VIII

SIGNIFICANT OBSERVATIONS IN FORTY-TWO FATALITIES DUE TO EPIDEMIC HEMORRHAGIC FEVER[a]

Case No.	Day of Death	Days after Initial Maximum Hematocrit	Phase at Death	Retroperitoneal Edema	1° Shock: Degree[b]	1° Shock: Maximum Hematocrit[c]	Transition Shock	2° Shock	Maximum Blood Urea Nitrogen[d]	Hypertension[e]	Hypervolemia	Severe Dehydration	Potassium Deficiency[f]	Hyperkalemia[g]	Hypernatremia[h]	Hyperpyrexia	Pulmonary[i]: Infection	Pulmonary[i]: Edema	Pulmonary[i]: Aspiration	Central Nervous System[j]	Remarks
38	4	Peak[k]	1° Shock	4+	4+	68			42									1+			Few petechial hemorrhages of midbrain, medulla and pons
5	5	Peak	1° Shock	4+	4+	56															
9	5	Peak	1° Shock	4+	4+	62			17							106.6					Terminal convulsion; old subdural hemorrhage
7	6	Peak	1° Shock	4+	4+	56			98												Terminal convulsion
1	6	Peak[m]	1° Shock	4+	4+																
26	6	Peak	1° Shock	4+	4+	58			69										Yes		
47	6	Peak	1° Shock	4+	4+	59			57									1+		Yes	Infarction of pons
21	6	Peak	1° Shock	4+	4+	59															
14	6	Peak[m]	1° Shock	4+	4+				24												
20	7	Peak	1° Shock		4+	62			85									1+			
30	7	1½	1° Shock	2+	4+	56															
39	7	Peak	Transition	2+	2+	50	4+		50									2+			Moderate focal edema and petechial hemorrhages
3	8	1½	Transition	2+	1+	58	4+		122												
4	8	1½	Transition	2+	2+	60	4+		117	1+							1+				
27	8	2	Transition	2+	4+	62	4+		128							107					
28	8	2	Transition	2+	4+	54	4+		58						Yes	107			Yes		Blood pressure maintained to death on continuous pressor drugs
23	8	2	Oliguric	0	1+	50		4+	74	1+						107	1+	1+			
45	8	4[m]	Oliguric	0	4+				146	2+	4+						2+	3+			Died suddenly in opisthotonus
8	9	3	Oliguric	0	2+	49			160	2+		Yes					4+	2+			Initial hematocrit 38; final, 26
12	10	Peak	1° Shock	4+	4+	67															Long initial febrile course; hematocrit increased on day 8
17	10	3	Transition	0	4+	62	4+					Yes						1+			
6	10	3	Oliguric	0	1+	51						Yes					4+				Terminal convulsion; initial hematocrit 39; final, 38
24	10	3	Oliguric	0	4+	62		4+		1+						108	1+				Pulmonary infection-bronchiolitis
25	10	4[m]	Oliguric	0	0				156	2+	4+	Yes		Yes			2+	4+			
41	10	3	1st Diuretic[n]	0	0	49				4+	4+						1+	4+			Terminal convulsion
10	11	5	Transition	2+	4+	52	4+		224			Yes		Yes			4+			Yes	Subarachnoid hemorrhage
2	11	5	Oliguric	0	1+	60			202			Yes	Yes								
13	11	5	Oliguric	0	1+	53		4+	220	2+		Yes					2+	2+			Terminal convulsion
31	11	5	Oliguric	0	4+	58	2+		184	2+		Yes	Yes						Yes	Yes	Hemorrhage pons
40	11	3	1st Diuretic	0	0	56			125	4+	4+						2+	4+		Yes	Cerebral angiitis, focal edema
16	11	5	4th Diuretic	0	1+	53			314				Yes				1+				
15	13	5	Oliguric	0	1+	50		4+	268	2+		Yes	Yes				4+	4+			
44	13	6	4th Diuretic	0	4+	56	4+	4+	218			Yes	Yes	Yes			4+	2+			Focal degeneration cortex and pons
46	13	7	4th Diuretic	0	2+	56		4+	232	2+	2+	Yes	Yes				4+	2+			
43	16	10	5th Diuretic	0	4+	66		4+	206	4+	4+	Yes	Yes	Yes			4+	2+			Convulsion, few small hemorrhages of cortex and basal ganglia
49	17	9	6th Diuretic	0	2+	60		4+	281	2+	2+	Yes		Yes						Yes	Petechial hemorrhages of cortex and basal ganglia
22	18	12	7th Diuretic	0	4+	56			230	1+					Yes		4+			Yes	Massive subarachnoid hemorrhage
11	18	12	9th Diuretic	0	4+	55		4+	250			Yes	Yes		Yes		4+	2+			
19	18	13	9th Diuretic	2+	2+	59		4+	274			Yes	Yes				4+	1+			
33	19	12	10th Diuretic	0	4+	68		4+	286	4+		Yes	Yes		Yes		4+	2+		Yes	Cerebral abscesses
29	23	13[m]	11th Diuretic	0	4+				244	4+		Yes	Yes		Yes						Hypocalcemia; terminal blood urea nitrogen 39
18	28	21	16th Diuretic	0	4+	60		4+	220	4+		Yes	Yes		Yes		4+	1+			Convulsions; blood urea nitrogen fell to 175, then rose to 329 terminally

See footnotes to Table VIII, page 637.

in two and hyperkalemia in another probably contributed to the shock while the terminal event in one was aspiration of vomitus. Of the twenty-three patients who died in the oliguric or diuretic phases, eleven died in late or secondary shock and one had several such episodes several days before death. Primary shock had occurred in all of these and transition phase shock in one. However, the earlier shock and capillary leakage had not been severe in half the patients dying in secondary shock. Dehydration, potassium deficiency, hypernatremia and pulmonary infections were common contributory factors to late shock. Three patients had no shock at any time during their disease, while another four had only mild or moderate shock. Important primary or contributing causes of death in patients who died without evidence of shock in the oliguric and diuretic phases included fluid and electrolyte abnormalities, pulmonary infection and edema, central nervous system involvement and perhaps "relative hypervolemia."[17]

SUMMARY

The complications observed in 828 cases of hemorrhagic fever, with their incidence, time of appearance, duration and sequelae, are described. Some of the clinical observations that may be related to the causes of these phenomena are discussed.

1. Sixteen per cent of the patients had clinical shock. One-third of these eventually died. Hypotension not associated with shock carried a good prognosis.

2. Hemorrhagic complications were encountered throughout the course of the disease but were rarely the primary cause of death.

3. Significant hypertension was encountered in 25 per cent of the patients during the oliguric and diuretic phases but was always transient.

4. Electrolyte disturbances were encountered during the oliguric and diuretic phases, hyponatremia and hyperkalemia being the most common.

5. Pulmonary edema was encountered during the oliguric and diuretic phases. Thirteen of fifteen patients with this complication expired. Evidence is presented that heart failure and excessive fluid intake did not contribute significantly to the pulmonary edema observed in this group of cases.

6. Central nervous system complications were observed most frequently during the oliguric and diuretic phases. Although central nervous system involvement contributed to the mortality, no neurologic residua were noted among the survivors.

7. Anemia was encountered in the convalescent phase in several patients and appeared to be related to the severity of the "uremic" phase rather than to blood loss.

8. Only sixteen of 783 surviving patients exhibited residua. Hyposthenuria and anemia were the most frequent.

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[a] Only factors considered to have contributed significantly to a fatal outcome are recorded. Factors regarded as primary or important in causing death are underlined. Items not underlined were present in considerable degree but were either no longer present at the time of death or were not considered to have contributed directly to death.

[b] 4+ = death in shock, or shock required continuous pressor drug therapy and/or more than 300 ml. concentrated human serum albumin; 2+ = occasional pressor drug therapy and/or 50 to 300 ml. concentrated human serum albumin required; 1+ = clinical shock that responds to simple measures such as shock blocks or leg-bandaging.

[c] Although maximum values in patients 6 and 8 were not greatly above normal, note (under Remarks) that initial and final hematocrits indicate considerable pre-existing anemia. Hemoconcentration in these patients was undoubtedly greater than that suggested by the maximum hematocrit values.

[d] Maximum values recorded when observations were made at frequent intervals. The maximum value occurred within a day or so of death in most patients.

[e] Four and frequently many more blood pressure values were recorded daily in most of the patients. Hypertension considered to be present if three-fourths or more of the blood pressure readings during one day exceeded 140/90 (exclusive of observations made during pressor drug therapy). 4+ = hypertension for more than four days with three or more levels of 160/100 or greater; 2+ = hypertension for more than two days with three or more levels of 150/90 or greater; 1+ = hypertension for one to two days.

[f] Although hypokalemia was prominent in only some patients designated "yes," significant depletion of body potassium stores is believed to have developed in all those so designated. These were all patients who had received little or no potassium-containing food or fluids for seven or more days and who vomited large amounts. Those in the diuretic phase also lost significant amounts of potassium in the urine.

[g] Recorded "yes" only if plasma potassium exceeded 6.5 mEq./L. and EKG exhibited severe alterations usually attributed to hyperkalemia.

[h] Recorded "yes" when serum sodium exceeded 155 mEq./L. for two or more consecutive days.

[i] Graded in severity as described in autopsy protocols, except where clinical protocol indicated unequivocal evidence for generalized pulmonary edema which cleared before death. Edema present only in areas of infection not recorded.

[j] Recorded "yes" only if findings at autopsy were described as extensive, and in patient 8 who died during a series of convulsions. Type and location of involvement described under Remarks.

[k] Peak-death within twenty-four hours after initial maximum hematocrit was reached.

[m] Precise time of maximum hematocrit not known. Days indicated are minimum possible number after a definite decrease in hematocrit.

[n] Number indicates day of diuresis on which death occurred.

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The Pathology of Thirty-nine Fatal Cases of Epidemic Hemorrhagic Fever*

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THE initial descriptions, in the Western medical literature, of the pathologic changes in epidemic hemorrhagic fever appeared in 1952 and 1953 in reports by Steer and Hullinghorst[1,2] on sixty-one fatal cases that occurred among the United Nations Forces in Korea during 1951. Kessler[3] independently described the gross pathologic changes in twenty-seven of these cases at approximately the same time. The characteristic findings were: (1) retroperitoneal edema; (2) diffuse hemorrhage in the right atrium of the heart; (3) severe congestion, hemorrhage and infarct-like necrosis in the renal medulla, and (4) hemorrhage and necrosis in the anterior lobe of the pituitary gland. Evidence of vascular damage was observed but no specific anatomic vascular lesion was found. The pathologic changes in the fatal cases of a similar disease that occurred in Manchuria between 1939 and 1945 had been previously described by Tokoro[4] and Kasahara[5] in the Japanese medical literature. Steer and Hullinghorst were able to establish fairly conclusively from pathologic material made available by Tokora and Kasahara that epidemic hemorrhagic fever, as observed in 1951, and the disease occurring in Manchuria were identical.

In 1952 also, Mayer,[6] in a detailed comparative analysis of the "Manchu-Korean" epidemic of hemorrhagic fever of the Japanese literature and the endemic hemorrhage nephroso-nephritis, observed in Siberia and described by the Russians, brought out the striking similarity between the two. The pathologic characteristics of the 1951 cases as reported by Steer and Hullinghorst[1,2] are almost identical with the descriptions of the lesions in Mayer's review.

The pathologic changes observed in thirty-nine fatal cases of epidemic hemorrhagic fever in 1952 form the basis of this presentation and are essentially similar to those described by Steer and Hullinghorst with the exception of a variation in the degree of necrosis in the renal medulla.

The clinical aspects of hemorrhagic fever are described elsewhere in this symposium by Sheedy and colleagues[7] who recognize five clinical phases of the disease, designated in their sequence of occurrence as follows: febrile, hypotensive, oliguric, diuretic and convalescent. In this presentation the pathologic changes will be considered in relation to the clinical phase of the disease that existed just before death in an attempt to determine the sequence of these changes.

MATERIAL AND METHODS

The autopsy material in thirty-nine of the forty-two fatal cases of hemorrhagic fever at the 8228th Mobile Surgical Army Hospital during the period of clinical observation specified in this symposium was reviewed at the First Medical Field Laboratory, Eighth Army, and form the basis of this presentation. Two pathologists performed all these autopsies and prepared the protocols. As a result of this experience they were able to provide more complete data than had been possible in the 1951 cases. These protocols, with extensive clinical summaries and representative tissue, were forwarded to the First Medical Field Laboratory, Army, for histopathologic study. Eleven other cases, not included in this study, were either not received at this laboratory or death occurred at another hospital.

The fixatives used were 10 per cent formalin, 5 per cent Zenker's acetic acid solution, and Regaud's solution. Representative tissue specimens from all organs were submitted and examined histologically, with infrequent exceptions. Hematoxylin and eosin was the routine stain. Giemsa's stain was used in conjunction

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with 5 per cent Zenker's acetic acid solution as the fixative in one-half of the cases for sections of the spleen, bone marrow, lymph nodes and liver.

The evaluation of the clinical course of the disease in the thirty-nine fatal cases here described is presented elsewhere in this symposium.[8] No deaths occurred in the febrile or convalescent phases. In order to separate a small group of cases in which there is no clear-cut delineation between the hypotensive and oliguric phases, it is necessary to include a transitional group.

TABLE 1
DURATION OF DISEASE IN THIRTY-NINE FATAL CASES OF HEMORRHAGIC FEVER IN 1952

Phase Groups	No. of Cases	Range of Duration (days)	Mean Duration (days)
Hypotensive	12	4–10	6
Transitional	5	8–11	8
Oliguric	9	8–13	10
Diuretic	13	10–28	17
All Groups	39	4–28	10

Clinical evaluation of the severity of shock is described by Giles et al.[8] The degree of shock was graded according to the duration of clinical shock and the therapy required and is recorded as severe (++++), moderate, (++) and mild (+). Shock was classified as primary, secondary and transitional,[8] although my preference would be the terms early and late, since primary and secondary as generally used have other specific connotations. Shock of more than one type was frequently recorded in the same patient. The term primary shock referred to the initial period of shock observed early in the disease, usually at the stage of defervescence, while shock in the later oliguric and diuretic phases, following an interval of normotension, was designated secondary shock. The term transitional shock indicates prolongation of the initial period of shock after the peak level of hematocrit had passed and hemoconcentration was subsiding.

The pathologic changes observed in the lungs, kidney, pituitary and adrenals, together with the incidence and degree of retroperitoneal edema, are recorded in the individual cases on the phase group reference tables. The duration of the disease, the degree and type of shock and the duration of the various phases are also indicated.

CLINICAL

The duration of disease in the thirty-nine fatal cases of hemorrhagic fever in 1952 varied from four to twenty-eight days, with an average duration of 10.9 days and a mean duration of 10 days. The range and mean duration of the cases comprising each phase group are recorded in Table 1.

Hypotensive Group. As already indicated, no deaths occurred in the febrile phase. The duration of the disease in the twelve cases of the hypotensive group varied from four to ten days and the clinical course was characterized by severe refractory shock of brief duration, with death occurring in shock after periods of eight to fifty-six hours. In nine of the twelve cases the total duration of shock was less than 36 hours. At the time of death hemoconcentration was most marked, with the hematocrit at the highest level observed during the course of the disease.

Transitional Group. The duration of disease in the five cases included in this group varied from eight to eleven days. Shock was more prolonged than in the previous group and varied from three to six days. The degree of prior primary shock had been severe in three while all cases exhibited a period of transitional shock which was classified as severe. Death occurred in shock with receding hemoconcentration one and one-half to five days after the peak hematocrit levels had passed. Azotemia was present, with levels of the blood urea nitrogen varying from 58 to 224 mg. per cent.

Oliguric Group. The duration of disease in the nine cases of the oliguric group varied from eight to thirteen days with death, usually in severe azotemia, after two to six days of oliguria. The preceding period of primary shock often was mild and of brief duration and in five cases it was recorded as slight or absent. Secondary shock, observed in only three cases, was severe and dominated the terminal stage. In one case (No. 25) neither primary nor secondary shock was recorded. Periods of hypertension during the oliguric phase were recorded in every case except one (No. 6). Convulsions occurred in three cases (Nos. 6, 8 and 13), usually in the terminal phase.

Diuretic Group. The duration of disease in the thirteen patients who died during the diuretic phase varied from ten to twenty-eight days and the length of diuresis from one to nine days.

Severe shock of either primary or secondary type was a prominent feature of the disease in ten cases, with secondary shock conspicuous in the terminal stage in eight cases. Clinical shock was not recorded in two cases. Diuresis usually began abruptly and was followed by fairly rapid reduction in the severity of azotemia unless secondary shock interfered. Severe azotemia was the outstanding feature, the blood urea nitrogen in eleven cases reaching maximum levels between 200 and 314 mg. per cent. Diuresis in some cases was associated with severe electrolyte imbalance.

PATHOLOGY

The pathologic changes observed in the thirty-nine fatal cases of hemorrhagic fever in 1952 consisted primarily of vascular alteration present in the cases of each group but was most intense in the hypotensive and transition groups. These vascular alterations were evidenced by intense capillary engorgement, diapedesis of erythrocytes, focal hemorrhages and altered capillary permeability. The altered capillary permeability was reflected by interstitial edema and retroperitoneal edema. The capillary engorgement and focal hemorrhages were widely distributed, involving many organs as well as the body surfaces including the skin, serosal surfaces and mucosal linings. Reaction of the tissue to hemorrhage in the form of cellular response, hemosiderin-laden macrophages or vascular proliferation was rarely encountered in any group. The intense congestion frequently was difficult to differentiate from recent hemorrhage, particularly in the renal medulla, and usually appeared as masses of fresh erythrocytes without discernible vascular walls. Morphologic changes within vessel walls were uncommon but when present usually consisted of prominence or increased cellularity of the endothelium with slight edema of the walls. No specific vascular lesion was observed in any of the cases included in this study. (Table II.)

Retroperitoneal Edema. The edema of the retroperitoneal tissue, as seen through the peritoneum, appeared as a translucent amber fluid and presented one of the most characteristic features of the hypotensive and transitional groups. It was of moderate to severe degree in fifteen of the seventeen cases in these groups and occurred in only one case of any other group. Retroperitoneal edema was observed in only three patients surviving beyond the eighth day of the disease; every patient in whom it was noted at autopsy had died in severe shock. The accumulation of fluid bulged the peritoneum anteriorly and involved the base of the mesentery, the perirenal adipose tissue and extended into the lateral peritoneal gutters. Microscopically, the edema appeared as homogeneous eosinophilic material between lobules of adipose tissue and in accumulations in the loose areolar connective tissue. Edematous material of similar appearance commonly was noted during this period of the disease in the epicardial fat, the submucosa of the small intestine and the peripancreatic fat.

Ascites of 100 to 400 ml. was described in nine cases, pleural effusion varying from 100 to 400 ml. in four cases; no pericardial effusion exceeding 100 ml. was recorded. Such manifestations were found predominantly among cases in the hypotensive and transitional groups.

The average weights of the various organs in each group are recorded in Table III. The incidence of the pathologic changes in each group is summarized in Table IV.

Cardiovascular System. The heart was usually of normal size and only two exceeded 400 gm. in weight. Slight to moderate dilatation of all the cardiac chambers was described in six cases, usually in association with a pale, greyish brown, flabby myocardium. Petechiae and ecchymoses, generally of mild degree, were commonly observed in the epicardium and were most prominent along the atrioventricular sulcus. Particularly striking on gross examination in thirty-one cases were the subendocardial hemorrhages in the right atrium and the right auricular appendage that appeared as a large confluent bluish-red thickened area (Fig. 1); in the other chambers they were small and infrequent. Microscopically, these hemorrhages appeared as masses of fresh erythrocytes resembling extreme congestion. Hemorrhage in the right atrium was severe and almost constant in the hypotensive and transitional groups. It was present in mild degree when death occurred late in the diuretic phase. The hemorrhage extended into the underlying myocardium, often associated with a slight mononuclear cellular response. In the majority of cases a wide zone of pale, swollen myocardial fibers lay under the endocardium of the right atrium and right ventricle, compressing the interstitial tissue and obliterating the space. Slight increase in cellularity of the endothelium without cellular

TABLE II

PATHOLOGIC CHANGES IN RELATION TO SHOCK AND DURATION OF DISEASE IN PHASE GROUPS OF FATAL HEMORRHAGIC FEVER

A. Hypotensive Phase Group

Case Number	Duration of Disease (days)	Shock*			Oliguria Duration (days)	Diuresis, Duration (days)	Retroperitoneal Edema	Lungs				Kidneys			Pituitary Necrosis	Adrenals	
		Primary	Secondary	Duration (days)				Edema	Bronchopneumonia	Abscess	Weight (gm.)	Epithelial Necrosis	Medullary Congestion	Weight (gm.)		Hemorrhage	Necrosis
38	4	++++	0	1			++++	+	0	0	650	0	++++	375	0	0	0
5	5	++++	0	2			++++	0	0	0	.....	0	++	...	+	0	+
9	5	++++	0	1			++++	0	0	0	.....	+	++++	...	+	++	++
7	6	++++	0	2			++++	0	0	0	.....	0	+	...	++++	++	++
26	6	++++	0	2			++++	0	0	0	875	0	++	400	0	0	0
47	6	++++	0	1			++++	+	0	0	1,400	0	++++	500	+	0	0
21	6	++++	0	1			++++	0	0	0	800	+	++++	400	Gross	0	0
14	6	++++	0	1			++++	0	0	0	625	0	++	425	0	0	0
20	7	++++	0	3			.....	+	0	0	800	0	++	400	0	0	0
30	7	++++	0	1			++	0	0	0	425	0	++	350	+	++	++
39	7	++	0	1			++	++	0	0	1,000	0	++++	325	0	0	0
12	10	++++	0	3			++++	0	0	0	.....	+	++++	...	0	+	+

B. Transitional Phase Group

4	8	+	0	3	..		++	0	+	0	...	0	++++	...	+	0	0
27	8	++	0	3	3		++	0	0	0	510	+	++	425	++	0	0
28	8	++++	0	3	2		++	0	0	0	700	0	++++	420	++	+	0
17	10	++++	0	5	4		0	+	0	0	775	0	++++	500	++++	+	+
10	11	++++	0	6	2		++	0	+	0	...	+	++++	...	+	0	0

C. Oliguric Phase Group

23	8	+	++++	4	5		0	+	+	+	750	+	++++	450	0	+	0
45	8	++++	0	2	3		0	+++	+++	0	1,300	0	++	300	0	+	0
8	9	++	0	2	4		0	++	++	0	.....	0	++++	...	Gross	0	0
6	10	+	0	1	3		0	++	++	+	.....	0	++++	...	++++	0	0
24	10	++++	++++	4	3		0	0	0	0	460	+	++++	450	Gross	0	0
25	10	0	0	0	2		0	++	++	0	1,450	+	++++	440	Gross	0	0
13	11	0	++++	1	2		0	0	0	0	.....	+	++++	...	++++	0	0
31	11	++++	0	1	6		0	0	0	0	575	0	++++	460	Gross	0	0
15	13	0	0	..	..		0	++	++	0	1,600	0	++++	670	Gross	0	0

D. Diuretic Phase Group

41	10	0	0	0	4	1	0	+++	+	0	1,200	0	++++	300	++++	0	0
40	11	0	0	0	3	1	0	++	+	0	1,775	0	++++	400	+	0	0
16	11	+	0	1	3	4	0	0	+	0	750	0	++++	500	++++	+	+
44	13	++++	++++	10	7	3	0	++	++	0	1,450	+	++++	300	+	0	+
46	13	++	++++	2	2	4	0	++	+++	+	1,350	+	++	400	++++	0	0
43	16	+	++++	1	5	..	0	++	++	0	1,450	0	++++	400	++++	0	+
49	17	++	++++	1	5	6	0	0	0	0	800	0	0	500	++	0	0
22	18	++++	0	2	5	6	0	0	+	++	650	0	++	400	Stromal collapse	+	0
11	18	++++	++++	8	7	8	0	+	+	0	.....	+	++	...	0	0	0
19	18	++	++++	1	5	8	++	+	+++	++	850	0	++++	400	++++	0	0
33	19	0	++++	2	7	7	0	+++	+++	+	2,400	0	++++	400	+	0	0
29	23	++++	0	4	4	9	0	0	0	0	350	0	++	280	+	0	0
18	28	++++	++++	11	6	9	0	+	+++	+	1,750	0	+++	400	Stromal collapse	0	0

* Transitional shock was recorded only in the Transitional Phase Group (B) where it was severe (++++) in every case.

infiltration or fibrin deposition was noted frequently in the endocardium of each chamber. In ten cases a few small perivascular and interstitial foci of mononuclear cell infiltration were seen in the myocardium, commonly in association with slight interstitial edema and focal

medulla, commonly visible on gross examination in the 1951 cases, were not observed. Microscopically intense congestion of the renal medulla was most prominent near the corticomedullary junction. (Fig. 3.) This characteristic manifestation has been described as a sea of fresh erythro-

TABLE III

ORGAN WEIGHTS IN PHASE GROUPS OF HEMORRHAGIC FEVER RECORDED AT AUTOPSY

Organ	Cases with Recorded Weights	Average Weight (gm.)	Weight Range for Group	Hypotensive Phase Group		Transitional Phase Group		Oliguric Phase Group		Diuretic Phase Group		Normal Weight Range[14] (gm.)
				No. of Cases	Average Weight (gm.)	No. of Cases	Average Weight (gm.)	No. of Cases	Average Weight (gm.)	No. of Cases	Average Weight (gm.)	
Heart	29	306	225–450	8	328	3	308	6	268	12	310	275–325
Lungs*	29	1,002	350–2,400	8	822	3	662	6	1,022	12	1,181	700–1,000
Spleen	28	162	50–500	8	211	3	175	5	180	12	119	125–175
Liver	30	1,807	1,300–2,750	8	1,665	3	1,700	7	1,836	12	1,894	1,500–1,700
Kidneys*	29	423	280–670	8	397	3	445	6	461	12	407	280–320
Brain	28	1,398	1,200–1,750	7	1,368	3	1,418	6	1,339	12	1,441	1,250–1,400

* The weights of the lungs and kidneys have been recorded as combined weights.

TABLE IV

INCIDENCE OF PATHOLOGIC CHANGES IN PHASE GROUPS OF FATAL HEMORRHAGIC FEVER

Phase Group	No. Cases	Lungs						Kidneys		Pituitary		Adrenals	
		Pulmonary Edema		Broncho-pneumonia		Abscesses		Epithelial Necrosis		Necrosis		Focal Necrosis	
		No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Hypotensive	12	4	33	0	0	0	0	3	25	6*	50	4	33
Transitional	5	1	20	2	40	0	0	2	40	5	100	2	40
Oliguric	9	6	67	6	67	2	22	4	44	7*	78	2	22
Diuretic	13	9	51	11	85	5	46	3	23	10	77	3	23
Total	39	20	51	19	48	7	17	12	30	28	72	11	28

* Includes cases with such typical gross changes that the specimens were used for museum purposes and not sectioned for microscopic examination.

degeneration or early necrosis of a single myocardial fiber or small groups of fibers. In no instance were these changes sufficiently marked to suggest the myocarditis of diphtheritic type described in the Japanese and Russian literature reviewed by Mayer.[6]

Kidneys. The kidneys were enlarged, with a pale grey to yellowish brown surface and a prominent, bulging, intensely congested, dark red medulla, contrasting with the pale greyish brown cortex. (Fig. 2.) Small areas of necrosis in the

cytes widely separating the medullary tubules. The loops of Henle and the collecting tubules were compressed and distorted, and at times only the pale necrotic outlines of a radiating tubule were discernible. The necrosis usually involved only small foci of tubular epithelium. At times it was associated with hemoglobin casts and resembled the necrosis of "lower nephron nephrosis." The epithelium in these foci was flattened, distorted and hypocellular, and the individual cells were small with a pyk-

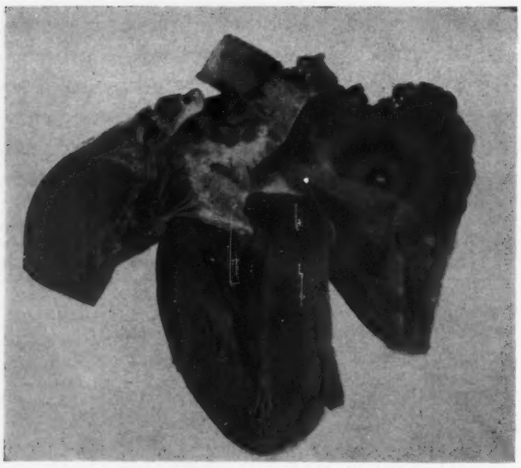

FIG. 1. Case 30 (AFIP Acc. 546385). Diffuse hemorrhages in the right atrium of the heart.

notic nucleus. Peritubular cellular infiltration was rarely encountered. Epithelial necrosis was limited to the medulla and occurred in eight (20 per cent) of the thirty-nine cases, fairly equally distributed among the groups. Cloudy swelling and hydropic degeneration of the proximal convoluted tubular epithelium with tubular lumina distended by abundant homogeneous eosinophilic material and hyaline casts were prominent in cases from the hypotensive, transitional and oliguric groups. In the diuretic group the proximal tubular lumina were usually dilated although devoid of contents. The epithelium was of average cellularity but the amount of cytoplasm was diminished. In several patients who died after prolonged diuresis the tubular epithelium was so flattened and hypocellular that it resembled an endothelial type lining. These cases did not exhibit the epithelial regeneration apparent in the other cases of this group. Interstitial edema of the renal cortex was common, especially in the oliguric group. The glomeruli were of average cellularity. Distention of Bowman's space by homogeneous eosinophilic deposits was common in the early phases of the disease. The epithelial cells of Bowman's capsule were enlarged and cuboidal.

Pituitary Gland. The pituitary was usually slightly enlarged and its infundibulum appeared deeply congested. The cut surface of the anterior lobe was described as congested, with pale yellowish-tan areas of necrosis frequently noted. Microscopically, in the hypotensive group the anterior lobe of the pituitary gland was diffusely and intensely congested, occasionally with one or several ill defined areas of early necrosis in which only the pale eosinophilic outlines of parenchymal cells remained. In the transitional, oliguric and diuretic groups, areas of necrosis were observed in almost every case after the ninth day of the disease. Usually they appeared as clearly demarcated foci of homogeneous eosinophilic material circumscribed by a distinct zone of sinusoidal hyperemia without cellular infiltration. These areas of necrosis generally were located in the central portion near the fibrovascular stalk of the infundibulum. If necrosis was severe, involving almost the entire central portion of the gland, a peripheral subcapsular zone of relatively uninvolved parenchymal cells remained. Focal necrosis in the anterior lobe of the pituitary gland, noted in twenty-eight (72 per cent) of the thirty-nine cases, closely paralleled the 77 per cent incidence of this change in the 1951 cases. After the ninth day of disease focal necrosis occurred in fourteen of the seventeen cases in the transitional, oliguric and diuretic groups; in two cases there were areas of stromal collapse. Necrosis was generally slight or absent in cases of the hypotensive group and slight or moderate in those of the transitional shock group. Pituitary glands from five of the nine cases of the oliguric group exhibited such characteristic gross changes that they were used as museum specimens and two others also exhibited extensive necrosis. Severe necrosis was most commonly observed in cases of the diuretic group although it was slight in four. In two cases in which death occurred at eighteen and twenty-eight days, respectively, small areas in the anterior lobe of the pituitary were devoid of parenchymal cells and consisted primarily of collapsed connective tissue stroma without cellular infiltration. They probably represented the residua of previous foci of necrosis.

Adrenal Glands. The adrenal glands were approximately of normal size with considerable reduction in cortical lipoid. In a few cases congestion of the sinusoids in the region of the zona reticularis was prominent but not intense. Focal necroses, usually of microscopic size, were observed in eleven (28 per cent) of the thirty-nine cases which were distributed rather equally among all groups. Large areas of necrosis were observed in three cases from the hypotensive group. Diffuse hemorrhagic necrosis involved one-third of the adrenal cortex in one case, and the superior third of both adrenal glands in two others. The adrenal medullae were little altered.

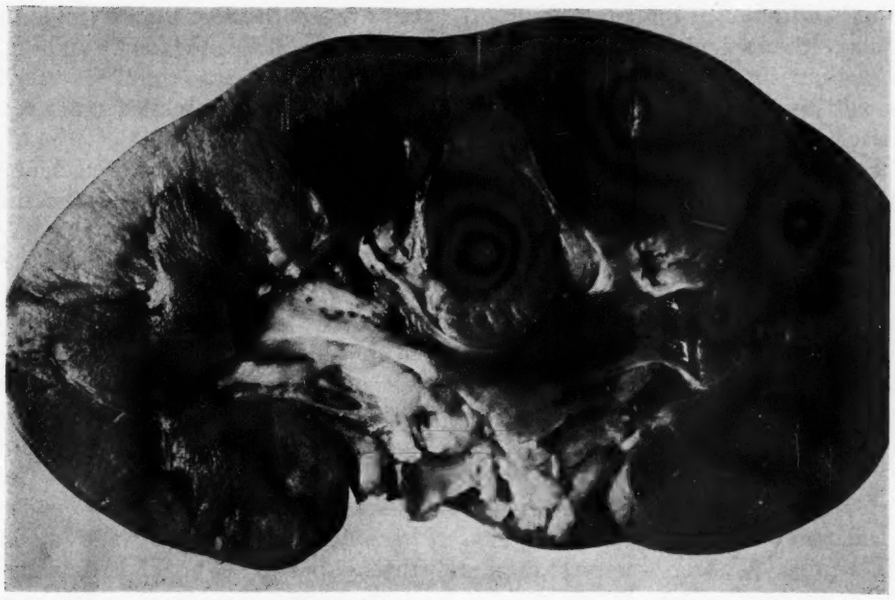

FIG. 2. Case 26 (AFIP Acc. 546381). On the cut surface of the kidney the intense congestion of the medulla contrasts sharply with the pale cortex. Note the subepithelial hemorrhages in the pelvis and calices.

Respiratory System. In the hypotensive and transitional groups the lungs were slightly congested and of little more than normal weight. Mild pulmonary edema was observed in five of the seventeen cases of the two groups and bronchopneumonia in two cases. In three of the nine cases of the oliguric group the lungs were distinctly heavier than normal. Edema was prominent in five cases and associated with moderate bronchopneumonia with very early abscess formation in two instances. Microscopically, pulmonary edema appeared as a deeply eosinophilic homogeneous material that contained scattered erythrocytes. Similar material was interspersed in areas of hemorrhage and bronchopneumonia, frequently with masses or isolated clumps of bacteria, especially in areas of early abscess formation. In the thirteen cases of the diuretic group, bronchopneumonia was associated with pulmonary edema of significant degree in eight cases in which death occurred between the tenth and sixteenth days. Abscess formation was associated with bronchopneumonia in five of the six patients who died in the diuretic phase later than the seventeenth day of disease. In one of these cases (No. 33) there was diffuse pulmonary aspergillosis with early abscess formation and multiple small metastatic abscesses in both cerebral hemispheres and in one kidney. Pulmonary aspiration was another complicating feature in two cases of the oliguric group and in one case of the hypotensive group.

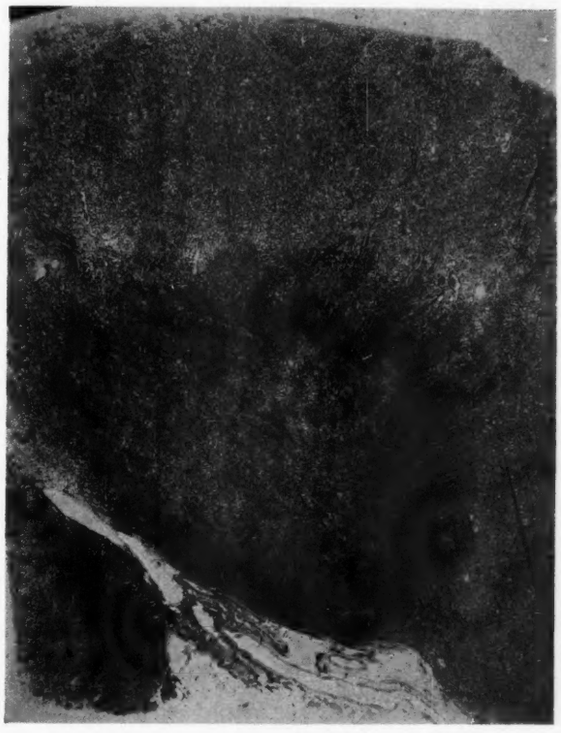

FIG. 3. Case 26. The intense congestion of the renal medulla is most striking near the corticomedullary junction. ×5.

Hematopoietic System. The spleen was usually of average size, exceeding 250 gm. in only two cases. In the hypotensive and transitional groups the cut surface of the spleen was bulging, soft

and dark red without prominent follicles. Microscopically, the splenic pulp exhibited intense congestion in which the sinusoidal pattern was not discernible. The follicles were of average size. There was a diffuse moderate increase in the cellularity of the splenic pulp in which numerous large mononuclear cells that resembled early myeloid elements formed clusters suggesting myelopoiesis. Subendothelial infiltration of trabecular veins by similar cells was commonly noted. Megakaryocytes were observed in only an occasional case and then were not numerous. In the other groups the spleens were generally smaller; microscopically, the follicles were small and the splenic pulp was of average cellularity and only slightly congested.

The lymph nodes were frequently described as grossly enlarged. Microscopically, mononuclear cells, similar to those observed in the splenic pulp, were seen within the medullary cords and in the sinusoids. In a few cases the sinusoids were distended with lymph and contained a few erythrocytes and numerous mononuclear cells. In the hypotensive phase, when retroperitoneal edema and interstitial edema were conspicuous, widely distended lymphatics were commonly observed in the submucosa of the small intestine and in the portal areas of the liver.

Bone marrow specimens, usually from both the lumbar vertebra and sternum, were available for study in thirty-seven cases. Intense congestion was a striking feature in the hypotensive and transitional groups, and often was associated with a moderate increase in cellularity of the marrow, with rather densely cellular foci with a predominance of myelopoiesis. Megakaryocytic hyperplasia was observed in twenty-two (60 per cent) of the thirty-seven cases, including eleven of twelve cases of the hypotensive group at the time that thrombocytopenia was most commonly observed. In three of these cases megakaryocytic hyperplasia was severe; in the other groups it was less common and almost invariably mild.

A total of fifty-two platelet determinations was recorded in twenty-nine cases, an average of 1.8 determinations per case, all performed between the fourth and twelfth days of the disease. Reduction in the platelet counts to less than 100,000 was recorded in seventeen (58 per cent) of the twenty-nine cases, generally between the fifth and eighth days. In the twelve cases without thrombocytopenia there were only two with more than a single platelet count recorded between the fourth and the eighth days.

Leukocytosis was commonly reported in this period of the disease and often reached leukemoid proportions.

Gastrointestinal Tract. Petechiae and ecchymoses, usually small, were the most common abnormalities observed in the gastrointestinal tract, occurring in thirty-one (80 per cent) of the thirty-nine cases. The hemorrhages were most numerous along the summits of the rugal folds in the body of the stomach, frequently forming a regular interconnecting linear pattern. Microscopically, the petechiae were situated in the most superficial portion of the lamina propria and usually appeared as laked blood that extended into the overlying epithelium. The hemorrhage was severe and almost confluent throughout the stomach in four cases in which death occurred on the seventh or eighth day of disease (two cases from the hypotensive group and two from the transitional group). In the presence of such extensive hemorrhages, 100 to 300 cc. of bright red blood was found in the stomach at the time of autopsy. Thrombocytopenia of 54,000 and 88,000 was recorded in two (Nos. 20 and 4) of the three cases with recorded platelet determinations, and megakaryocytic hyperplasia of the bone marrow was noted in postmortem specimens from both. Gastrointestinal hemorrhage of 500 cc. was described in one patient from the oliguric group who had severe azotemia with multiple superficial gastric mucosal ulcerations.

Liver and Gallbladder. The liver was of average size in the early phase of the disease and enlarged in the oliguric and diuretic phases, four of the twelve from the latter group exceeding 2,000 gm. Passive hyperemia of the liver, although common, was seldom marked. Focal necrosis, generally mild, occurred in thirteen (33 per cent) of the thirty-nine cases and usually involved only small mid-zonal portions of a hepatic lobule, occasionally associated with a slight mononuclear cell infiltration. In two cases areas of necrosis were numerous and frequently confluent. Diffuse parenchymal cell degeneration, generally in the form of early fatty metamorphosis, was commonly observed. A few mononuclear cells, similar to those in the hematopoietic system, were scattered throughout the portal areas. Edema of the wall of the gallbladder, though infrequent, was the only pathologic change observed in the biliary tract.

Pancreas. In the hypotensive and transitional groups slight capillary congestion frequently was evident in association with edema of the peripancreatic and perilobular connective tissue. Dilatation of the pancreatic acini and intralobular pancreatic ducts, as described by Baggenstoss[9] in uremia and dehydration, was noted in thirteen (36 per cent) of the thirty-six cases in which tissue was available for microscopic examination. It was most severe in the seven patients of the diuretic group in whom azotemia and dehydration were prominent. A sparse mononuclear and neutrophilic leukocytic infiltration frequently accompanied edema and ductal dilatation, and small foci of necrosis were seen in the case with the most severe lesions.

Central Nervous System. In the central nervous system hemorrhagic phenomena, usually scattered petechiae, were observed in sixteen (41 per cent) of the thirty-nine cases, with roughly equal distribution in all groups. The most prominent hemorrhagic lesions occurred in five patients who died during the oliguric or diuretic phase, between the tenth and the eighteenth day of disease. Petechiae were seen in the pons and medulla in three cases; diffuse massive petechial hemorrhages were noted throughout both cerebral hemispheres in one, and extensive subarachnoid hemorrhage about the pons and cerebellum in another (No. 22). The brain was of average size early in the disease and heavy later. Cerebral edema was marked in six cases in which brain weight exceeded 1,500 gm., five of them from the oliguric and diuretic groups.

Skin and Muscle. Increased prominence of the vessels of the subpapillary portion of the corium, accompanied by a slight perivascular infiltration of mononuclear cells, as described by Steer and Hullinghorst,[1] was seen in the 1952 cases.

Small perivascular aggregates of mononuclear cells were occasionally noted in striated muscle, although no changes were apparent in the vessel walls. In a few cases there was granular or hyaline degeneration of the muscle fibers.

CAUSES OF DEATH

In the seventeen cases of the hypotensive and transitional groups persistent shock that had become refractory to therapy was the major factor in the cause of the death; however, pulmonary aspiration of gastric contents was the immediate cause in one case and hyperkalemia in another.

In the nine cases with varying degrees of azotemia making up the oliguric group death was attributed to a combination of pulmonary edema and bronchopneumonia in six cases, with pulmonary abscess formation an added feature in two. Recurrent severe secondary shock was the precipitating factor in two (Nos. 13 and 24) of the three remaining cases, and pulmonary aspiration in the third (No. 13). Death was abrupt in one case (No. 25) with pulmonary complications in which there was clinical evidence of hyperkalemia.

In the thirteen cases of the diuretic group, azotemia was receding but still often severe. Pulmonary complications continued to be the major factor in causing death. Eight of the thirteen cases exhibited significant degrees of combined pulmonary edema and bronchopneumonia, with superimposed abscesses in five. In one case (No. 19) death resulted from pulmonary aspergillosis with metastatic renal and cerebral abscesses. Severe secondary shock was also an important factor in six cases with pulmonary complications and the major factor in two cases (Nos. 11 and 49). Death apparently resulted from prolonged diuresis with electrolyte imbalance in one case (No. 29), diffuse subarachnoid hemorrhage about the pons and the cerebellum in another (No. 22) and cerebral edema during severe azotemia in a third (No. 16).

DISCUSSION

The pathologic changes in the thirty-nine fatal cases of hemorrhagic fever in 1952 closely resemble the descriptions of the 1951 cases by Steer and Hullinghorst[1,2] and those in Mayer's review[6] of the Japanese and Russian literature, supporting the general belief that the diseases observed in Korea, Manchuria and Siberia are the same entity. Although no specific vascular lesion has been found in the 1952 cases, the pattern of the pathologic changes strongly suggests that vascular damage constitutes the basic disease process. The etiology and mechanism of this vascular injury are unknown. Search for etiologic agents in the cases of this presentation was limited primarily to stains for rickettsia. Although this study was fruitless, it was not sufficiently complete to justify any conclusions. The pattern of pathologic change observed does not resemble that of any other disease in the experience of this author.

The prominence of capillary engorgement, diapedesis of erythrocytes, focal hemorrhages throughout the parenchymal organs and serosal

and mucosal surfaces, and the altered capillary permeability reflect vascular damage. Somewhat similar changes were observed by Moon[10] in secondary shock of various etiologies and he considered them to be evidence of endothelial damage. The retroperitoneal edema characteristic of the initial period of shock in hemorrhagic fever suggests severe vascular damage. This manifestation of altered capillary permeability was not described by Moon in secondary shock of various duration nor did he mention the severe congestion and hemorrhage in the renal medulla or the hemorrhage in the right atrium of the heart that are such constant features in fatal cases of hemorrhagic fever. These changes, although varying in extent, are seen in every stage of hemorrhagic fever even when death occurs in the absence of shock.

The most prominent clinical features of the disease from the fifth to the ninth day, i.e., hypotension and shock with hemoconcentration, probably result from vascular damage with severe congestion and increased vascular permeability. The rare occurrence of retroperitoneal edema in patients living beyond the eighth day of the disease, coincident with the recession of hemoconcentration, suggests that the primary vascular damage had subsided. Secondary shock later in the disease was generally not accompanied by retroperitoneal edema. The absence of retroperitoneal and interstitial edema in the oliguric group coupled with the sudden appearance and increased incidence of pulmonary edema suggests that the abnormal interstitial fluid is resorbed and redistributed at the end of the initial period of shock.

The coexistence of bronchopneumonia and pulmonary edema in many late cases, often associated with abscess formation, may indicate that the proteinaceous fluid provides a fertile medium for bacterial growth. This has been suggested by Moon[11] who noted similar lesions occurring approximately forty-eight hours after the onset of secondary shock in cases with the pulmonary edema described as albuminous in appearance. The exudate of the bronchopneumonia contained an abundance of proteinaceous and fibrinous material intermixed with polymorphonuclear leukocytes and bacteria, often with the formation of bacterial colonies. Necrosis of the alveolar walls and abscess formation are frequent findings that are inconsistent with the degree of cellular response exhibited.

Evaluation of the role of shock in production of the typical renal lesion is aided by several significant clinical observations. The albuminuria early in the disease that commonly precedes the onset of shock may be evidence of the generalized capillary involvement.[8,12] In addition, oliguria has been noted to develop in the absence of hypotension.[8] Congestion of the renal medulla was described by Moon in secondary shock but not of the intensity that is such a striking and constant feature in hemorrhagic fever. It is suggested that the medullary congestion and hemorrhage are the result of vascular damage and the ensuing shock is a contributing factor. The variable tubular epithelial necrosis, hemoglobin casts and the focal necrosis observed in the renal medulla in the 1951 cases[1–3] are considered secondary to anoxemia resulting from both factors. Moreover, reduction in renal function without necrosis may result from transient alterations in epithelial cellular metabolism due to the anoxemia of stasis and increased tissue tension in the medulla Persistence of medullary congestion in the diuretic group and the recurrence of shock undoubtedly are significant factors delaying the regeneration of tubular epithelium and return of normal function. However, it is not possible in this small group of cases to evaluate the factors that influence regeneration of tubular epithelium in hemorrhagic fever.

Analysis of the role of shock in the production of necrosis in the anterior lobe of the pituitary gland seems to indicate that shock is not the only major factor. According to Sheehan and Murdock[13] there is a definite relationship between the size and frequency of postpartum pituitary necrosis and the severity of shock, occurring in those patients who survived more than fourteen hours after delivery. In the hypotensive group of hemorrhagic fever, however, pituitary necrosis was least frequent when shock was most severe and had persisted from eighteen to thirty-six hours. It is possible that the time which elapsed after cellular death in these cases may have been insufficient for development of recognizable histologic changes. Furthermore, the lesion was noted in several cases of the diuretic group in the absence of previous shock and was present in almost every case after the ninth day of disease regardless of the severity and duration of preceding shock.

Since the blood supply of the pituitary is primarily venous in origin and derived from the hypophyseal-portal system, it is my belief that,

in the absence of shock, necrosis may occur as a result of anoxemia from stasis due to capillary damage. The characteristic intense congestion of the anterior lobe and the infundibulum of the pituitary, a manifestation of stasis in a hypophyseal-portal system, supports this concept. An addition factor may be increased susceptibility of the parenchymal cells to anoxemia during stress. The necrosis in the adrenals and liver is probably more directly related to shock than vascular damage, since Moon has noted it frequently in secondary shock.

The relationship of thrombocytopenia to the vascular damage is not clear and platelet determinations were not sufficiently numerous to allow a general conclusion. However, the high incidence of thrombocytopenia recorded predominatly between the fourth and eighth day and the frequency of megakaryocytic hyperplasia in autopsy specimens from all groups strongly suggest that thrombocytopenia may be a significant factor. This may contribute particularly to the development of gastrointestinal hemorrhage which is severe only during this period.

The association of significant hemorrhagic phenomena in the central nervous system and cerebral edema in the oliguric and diuretic phases with episodes of hypertension is suggested but cannot be proved because these lesions are infrequent.

SUMMARY

The pathologic changes observed in thirty-nine fatal cases of hemorrhagic fever in 1952 have been studied in the light of the significant clinical data. The cases have been grouped according to the clinical phase in which death occurred in an attempt to determine the sequential development of the pathologic changes and to evaluate the role of shock in their pathogenesis. Several conclusions resulting from this correlation of clinical and pathologic data seem clearly evident.

The almost constant occurrence of hemorrhage in the right atrium of the heart, of severe congestion of the renal medulla, and of congestion and infarct-like necrosis in the anterior lobe of the pituitary gland, in association with the pattern of the vascular changes, supports the contention proposed in the Japanese literature and by Steer and Hullinghorst[1,2] that capillary damage is the basic process. Retroperitoneal edema, observed only once in secondary shock, is the striking pathologic feature when the patient dies during shock in early phases of the disease. It is rarely encountered after the eighth day when the initial shock usually terminates, suggesting that vascular damage has subsided. Recurrent shock in the later phases of the disease is due to other contributing factors.

The abrupt increase in incidence of pulmonary edema in the oliguric phase, particularly after the eighth day of the disease when retroperitoneal edema is rare, supports the clinically suspected role of redistribution of fluid and electrolytes coincident with resorption of the abnormal interstitial fluid.

The frequent coexistence of pulmonary edema and bronchopneumonia in the oliguric and diuretic groups and the high incidence of pulmonary abscess formation support the concept of Moon that pulmonary edema of the albuminous type is conducive to the development of pulmonary infections.

The almost constant presence of necrosis of the anterior lobe of the pituitary gland in cases of more than nine days' duration, irrespective of occurrence, type or duration of preceding shock, strongly suggests that shock is not the only major factor in the pathogenesis of pituitary necrosis in hemorrhagic fever. Anoxemia from severe congestion and stasis resulting from vascular damage is also an important factor and probably is the major cause of necrosis in the absence of shock.

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Observations on the Hemostatic Defect in Epidemic Hemorrhagic Fever*

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DESCRIPTIONS of the hematologic changes associated with hemorrhagic fever have appeared in published reports of the disease.[1,2] These include increases in hemoglobin concentration, hematocrit and leukocyte and erythrocyte counts toward the end of the febrile phase and during the shock phase. Increased numbers of immature granulocytes are found in the peripheral blood during the febrile and shock phases whereas mature granulocytic elements and abnormal lymphocytic forms resembling Downey cells accompanying an absolute lymphocytosis are common during the oliguric and convalescent phase. All these observations have been confirmed by the present author but need not be reported here.

Previous studies on the hemorrhagic aspect of the disease further revealed increased capillary fragility (positive Rumpel-Leede's test) during the early phases, increased bleeding time and decreased platelet counts between the third to the tenth or twelfth day of the disease. Prothrombin time and coagulation time have been reported to be normal.[1,2] Bone marrow aspiration studies and examinations of postmortem marrow specimens have revealed hyperplasia during the febrile and hypotensive phases.[1,3]

The purpose of the present paper is to describe further observations on the factors concerned with coagulation during the course of hemorrhagic fever.

CLINICAL MATERIALS AND METHODS

All observations were made at the Hemorrhagic Fever Center in Korea during the fall of 1952. Of the twenty-nine patients studied nineteen had a mild course, four a moderately severe course and six a severe course. Two patients in the latter group succumbed. Frequent platelet counts and other coagulation studies were made in all twenty-nine patients, often daily. The platelets were enumerated in a counting chamber using Rees-Ecker solution as a diluent. Prothrombin times were determined by the one-stage procedure of Quick. The normal time (100 per cent value) by this method was between twelve and thirteen seconds. Clotting times were determined by the Lee-White method, the last tube to clot being taken to indicate the clotting time. Prothrombin consumption was determined sixty minutes after clotting by the method of Stefanini and Crosby.[4] Clot retraction was measured by noting the amount of retraction after one hour of incubation at 37°C.

RESULTS

The most frequently observed abnormality in the coagulation mechanism was a depression of the platelet count. Every patient studied had a moderate thrombocytopenia with platelet counts in the vicinity of 100,000 per cu. mm. during the early phase of the illness when fever was present and before hypotension had developed. Abnormal platelet forms were observed in smears of the peripheral blood at the time thrombocytopenia was present. Many platelets were abnormally large. Clotting times were within the normal range (four to ten minutes) during this phase. Six patients had diminished prothrombin activity during the febrile phase but in only two instances was it below 60 per cent of the normal. It was during this febrile stage that skin, palatal and conjunctival petechiae appeared. No clinically serious bleeding was observed in any of the present patients during this phase.

A hypotensive or shock phase was observed in fourteen patients. The platelet count in most patients remained below normal during the hypotensive phase and was as low as 25,000

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per cu. mm. in two patients in severe shock. Three patients, including those already mentioned, had clotting times in excess of twenty minutes and prothrombin activities of 50 per cent or less of normal during periods of prolonged and severe shock. In two of these patients external evidence of considerable bleeding developed. Altogether, five patients had prolongation of the clotting time during the hypotensive phase. All fourteen patients who had a recognized hypotensive episode had prothrombin concentrations of 80 per cent or less of normal during the period of hypotension. Bleeding of serious clinical consequence occurred in one patient during shock at a time when the clotting time was in excess of twenty minutes, prothrombin activity 40 per cent of normal and the patelet count in the range of 40,000 to 70,000 per cu. mm.

Special studies employing normal plasma and normal plasma treated with calcium phosphate gel (deficient in prothrombin and stable factor) were made on the plasma of one patient. This plasma was obtained during a period of shock when the prothrombin activity was 50 per cent of normal, clotting time twenty-two minutes and the platelet count 25,000 per cu. mm. Although the presence of a small amount of circulating anticoagulant could not be excluded with certainty, these studies clearly demonstrated that both prothrombin and the stable factor were significantly decreased in this plasma.

During the oliguric phase the prothrombin activity returned promptly to normal in all but one patient. In this patient jaundice and hepatomegaly developed and concurrent hepatitis was suspected. The clotting time returned to normal in all patients. However, during the oliguric phase the platelet count remained at 150,000 per cu. mm. or below in all but three patients. Evidence of a bleeding tendency persisted throughout the oliguric phase in some patients.

Five of the seven patients who had a severe or moderately severe hypotensive episode and in whom hypertension subsequently developed during the oliguric phase had one or more manifestations of external bleeding such as epistaxis, hematemesis, purpura, melena or gross hematuria. These hemorrhagic phenomena occurred during the hypertensive period. Platelet counts in these five patients were below normal, four having counts below 100,000 per cu. mm. at the time the bleeding occurred. Factors contributing to the bleeding during the hypertensive period included physical trauma associated with vomiting, retching, marked restlessness and convulsive episodes. It would seem likely that these factors in conjunction with the thrombocytopenia could adequately explain the hemorrhagic manifestations observed at this stage of the disease. However, the possibility of persistent capillary damage cannot be excluded.

Clot retraction studies were not particularly revealing. Poor clot retraction was consistently associated with decreased platelet counts. Thirteen prothrombin consumption determinations were performed with blood obtained from five patients. In all instances the prothrombin utilization was within the normal range. This would indicate that there was no defect in the formation or concentration of thromboplastin. None of these patients, however, had extremely low platelet counts at the time the test was done.

COMMENTS

Several possible explanations for the persistent thrombocytopenia observed in epidemic hemorrhagic fever can be offered. Bone marrow aspirations were not made during this study but a previous report[1] indicated that increased numbers of megakaryocytes may be found in the marrow. Abnormal platelets are found, similar to those seen in other thrombocytopenic diseases. It is possible that increased platelet destruction occurs. This could result from widespread capillary damage, to which the increased transudation of plasma which occurs during this disease[5,6] is attributed. Platelet agglutination associated with the appearance of autoimmune antibodies is also a distinct possibility although it has not been studied. The thrombocytopenia, together with capillary damage, would seem to explain adequately the bleeding which is observed in hemorrhagic fever, particularly when mechanical stresses such as vomiting and convulsions occur concurrently. The coagulation defect found in this disease during the period of renal insufficiency may be similar to the defect which has been observed in acute post-traumatic renal insufficiency.[7] This is particularly true in the severely ill individual and may contribute materially to the bleeding seen in these patients.

SUMMARY

Studies of the coagulation mechanism in epidemic hemorrhagic fever reveal abnormalities

in prothrombin activity, clotting time and platelet count. Persistence of thrombocytopenia, which develops early in the disease, through the oliguric-hypertensive phase would appear to be causally related to the bleeding phenomena observed. Occasional marked deficiencies in plasma coagulation factors are found in seriously ill patients and may contribute to clinically significant bleeding. This plasma coagulation defect is similar to that observed in acute renal insufficiency and has not been clearly defined.

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Blood Volume in Epidemic Hemorrhagic Fever*

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HEMORRHAGIC fever is characterized by a febrile phase of four to six days' duration followed by a hypotensive phase and then a period of renal insufficiency. Shock occurs in approximately 16 per cent of the cases at the time of defervescence and has been responsible for over one-third of the deaths.[1] There is much evidence that the shock occurring during some severe infections is due to loss of vascular tone with little or no change in blood volume.[2–4] In hemorrhagic fever, however, diminution in plasma volume has been considered to be a major factor in the development of shock. An increase in hematocrit with no increase in total serum proteins together with marked retroperitoneal edema in patients dying in shock[5–8] are indirect evidence for plasma loss by capillary leakage.

A study of blood and plasma volume during the different phases of hemorrhagic fever was therefore undertaken. The T-1824 (Evans blue dye) method was chosen because of its simplicity and ready adaptability to use in an army field hospital; moreover, the disappearance rate of the dye from the plasma would serve as an index of capillary permeability and plasma leakage.[9] In addition, the blood volume was measured in a smaller number of patients by the tagged (P-32) red cell technic. Comparison of volumes as measured by the two technics was made in a few patients.

MATERIALS AND METHODS

Studies with T-1824. Control blood volume determinations were made in five young adult males of the laboratory staff who were in good health and in four who had had malaria. All determinations in the latter group were performed after they had been afebrile and asymptomatic for forty-eight hours or longer.

Eight of the patients with hemorrhagic fever were studied while in clinical shock. Although the severity of the shock varied considerably, these patients had several or all of the following criteria of shock: systolic arterial pressure of 85 mm. Hg or less, weak or absent radial pulsation, heart rate of 120 per minute or higher, warm and moist skin later becoming cold and pale or cyanotic, and prolonged blanching time of the skin. All had increased hematocrits during the shock phase but not necessarily at the time of study.

The treatment varied according to the severity of shock. Three patients required two to four units of albumin intravenously (human concentrated salt-poor albumin, 25 gm. per 100 cc. unit) to control their hypotension. The five remaining patients were treated throughout the shock phase with constant intravenous infusions of L-arterenol. One of these had only mild shock which required no supplementary therapy, four were in severe shock and required albumin in addition to L-arterenol.

Studies in patients who had no shock were also made. Of these four were thought to have disease of moderate severity with increased hematocrits during the hypotensive phase and maximum blood urea nitrogen values ranging from 95 to 160 mg. per cent, although none of these had blood pressures less than 100/60. Nine patients were considered to have mild hemorrhagic fever, generally with relatively small increases in hematocrit and maximum blood urea nitrogen values that ranged from normal to 90 mg. per cent.

Finally, several studies were made during late

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convalescence in four patients who had had severe hemorrhagic fever. All had had severe azotemia with blood urea nitrogen values exceeding 250 mg. per cent and presented evidence of residual renal damage during their prolonged convalescence, with hyposthenuria, polyuria and nocturia. In addition two were anemic at the time of study.

In all cases the blood volume determinations were made under the best basal conditions possible and before intravenous therapy was started.

The plasma volume determinations were performed with the Evans blue dye (T-1824*) with a technic modified from that of Gregersen.[10–13] The dye-tinged specimens were collected without stasis from the antecubital vein opposite that used for the dye injection at ten-minute intervals for an hour following injection. Dye-tinged plasma standards were prepared for every determination during the first half of the study until it became obvious that the standard curves were identical for all plasmas, whether from azotemic patients or not. The mean and standard deviation of the K values determined in forty-two separate plasmas was 118 ± 4 (fifteen of these were azotemic with blood urea nitrogen values ranging up to 190 mg. per cent). Thereafter the standard curve was determined only when a new lot of dye was used.

Total blood volumes (TBV) were calculated from the equation:

$$TBV = \frac{PV}{100 - (Hct \times 0.960)} \times 100$$

where Hct is the hematocrit (Wintrobe method) and 0.960 is the correction factor for trapped plasma.[14] Total plasma proteins were estimated from the plasma specific gravities obtained by the copper sulfate method.

The disappearance rate[15] is defined as the percentage of dye lost from the circulating plasma during the first hour:

$$DR = \frac{C_0 - C_{60}}{C_0} \times 100$$

where C_0 and C_{60} are the dye concentrations at 0 and 60 minutes, respectively.

Studies with Tagged (P-32) Red Cells. Blood volumes were measured by a slight variation of the Reeve-Veall P-32 technic[16] in four normal subjects and twelve patients in various phases of hemorrhagic fever. Simultaneous measurements with the T-1824 and the P-32 technics were made in seven of the studies.

Approximately 15 ml. of the patient's blood was incubated with 30 μc. of P-32 in the form of sodium phosphate. This was obtained from Abbott Laboratories and had been preassayed and sterilized. The incubation process was carried out at 37°C. for two hours. The cells then were washed three times and resuspended in isotonic saline solution. A calibrated 5 ml. syringe was used for injection of the tagged cell suspension and for preparation of the standard. Two 10 ml. venous blood samples were withdrawn from the patient after permitting adequate mixing of the injected tagged red blood cells. Five ml. of bank blood was added to the standard after appropriate dilution. The red blood cells were hemolyzed by dilution with distilled water prior to the counting procedure. The standard and samples were each counted for a total of 2,000 counts. All counts were corrected for background and for dilution. Red blood cell volumes (RBV) and plasma volumes (PV) were calculated by using the hematocrit value corrected for trapped plasma.

RESULTS

T-1824 Technic. The mean plasma volume and standard deviation in ten experiments in nine control subjects was 44.2 ± 6.1 ml./kg. body weight, the mean red cell volume was 34.0 ± 5.0 ml./kg., and the mean total blood volume was 78.9 ± 10 ml./kg. These values compare favorably with the findings of Wasserman et al.[17] who reported a mean plasma volume of 42.1 ± 5.8 ml./kg., a mean red cell volume of 27.7 ± 3.6 ml./kg. and a mean total blood volume of 69.8 ± 8.3 ml./kg.

The results of all the T-1824 determinations are summarized in Table 1. The serial changes in blood volume in these patients are presented in Figures 1, 2 and 3, and the dye disappearance rates in Figure 4.

Two of the eight severely ill patients died in irreversible shock with marked reductions in plasma volume to 30.4 and 31 ml./kg. body weight. Of the six patients who survived shock three exhibited low plasma volume during shock, ranging from 29.5 to 31.2 ml./kg., whereas the other three had normal plasma volumes, ranging from 40.8 to 45.0 ml./kg. body weight. However, during the phases subsequent to shock the plasma volume of all patients in this

* Supplied in 5 ml. ampuls with exactly 25 mg. per ampul.

TABLE I

T-1824 BLOOD VOLUMES AND DISAPPEARANCE RATES IN HEMORRHAGIC FEVER

Patient	Day of Illness	Phase of Illness	Weight (kg.)	Corrected Hematocrit†	Blood Volumes*			Dye Disappearance Rate (% 1 hr.)
					Plasma (ml./kg.)	Red Cells (ml./kg.)	Total (ml./kg.)	
				Severely Ill Group				
H. F.	5	Febrile	77.2	46	40.8	34.9	75.7	3.1
	11	Diuretic	75.0	37	47.0	28.0	75.0	0.4
	23	Convalescent	75.9	37	50.2	30.0	80.2	1.9
P. C.‡	4	Shock	55.0	61	30.4	48.6	79.0	23.0
H. H.	6	Shock	73.6	36	29.5	16.2	45.7	24.0
	8	Oliguric	73.6	24	42.5	13.3	55.8	11.0
	41	Convalescent	63.1	28	41.5	15.9	57.4	11.0
G. O.	6	Shock	75.5	47	30.4	26.9	57.3	10.0
	9	Oliguric	69.5	34	41.2	20.8	62.0	3.1
	33	Convalescent	63.1	27	42.6	15.6	58.2	6.6
V. R.	5	Febrile	62.6	48	41.4	38.3	79.7	11.0
	6	Shock	58.1	52	42.0	45.0	87.0	12.0
	20	Diuretic	56.8	28	54.1	14.7	68.8	1.0
	35	Convalescent	57.2	35	54.4	28.6	83.0	1.0
S. M.	4	Shock	72.7	56	31.2	39.0	70.2	1.0
	15	Convalescent	72.7	34	55.0	28.3	83.3	1.0
P. T.‡	4	Shock	75.9	54	31.0	35.9	66.9	9.4
H. S.	6	Shock	76.4	47	41.1	36.4	77.5	1.5
	22	Convalescent	72.7	37	46.8	27.9	74.7	0.3
E. G.	28	Convalescent	74.0	24	43.1	13.6	56.7	0.3
	36	Convalescent	70.0	35	41.9	22.1	64.0	6.1
A. C.	60	Convalescent	71.4	36	58.1	32.0	90.1	0.3
	70	Convalescent	72.7	43	44.4	33.8	78.2	3.0
S. M.	90	Convalescent	58.6	31	48.8	21.7	70.5	12.0
	96	Convalescent	58.1	32	44.8	20.8	65.6	4.0
T. H.	106	Convalescent	60.6	45	40.1	33.2	73.3	0.3
	115	Convalescent	58.1	42	39.0	28.6	67.6	3.0
				Moderately Ill Group				
E. T.	6	Hypotensive§	73.6	53	34.3	38.4	72.7	20.0
	10	Oliguric	70.9	38	42.9	26.6	69.5	13.0
	15	Diuretic	68.6	45	53.5	44.0	97.5	0.4
	45	Convalescent	78.4	43	54.6	40.8	95.4	0.9
B. T.	6	Hypotensive§	60.0	56	44.2	55.3	99.5	5.4
	10	Diuretic	56.0	56	42.1	52.9	95.0	1.0
J. T.	5	Febrile	73.1	45	44.9	36.9	81.8	1.7
	7	Oliguric	73.1	46	36.2	31.0	67.2	0.8
	9	Diuretic	73.1	33	53.2	25.8	79.0	0.3
R. B.	3	Febrile	70.5	49	43.3	41.6	84.9	5.6
	6	Oliguric	65.9	43	48.6	37.0	85.6	2.4
				Mildly Ill Group				
J. B.	7	Febrile	61.8	41	46.8	32.1	78.9	14.0
J. I.	6	Diuretic	80.0	42	41.6	30.4	72.0	3.0
A. D.	5	Hypotensive§	72.7	51	39.2	40.6	79.8	6.0
	11	Diuretic	66.8	50	34.7	34.4	69.1	1.0
	20	Convalescent	77.3	39	37.4	24.2	61.6	10.0
J. P.	5	Febrile	75.9	48	45.9	42.3	88.2	0.3
	15	Convalescent	72.7	40	50.0	33.6	83.6	2.6
W. T.	5	Febrile	66.5	37	56.6	33.6	90.2	0.4
	13	Convalescent	65.5	35	59.0	31.3	90.3	0.4

TABLE I (*Mildly Ill Group—Continued*)

Patient	Day of Illness	Phase of Illness	Weight (kg.)	Corrected Hematocrit†	Blood Volumes*			Dye Disappearance Rate (% 1 hr.)
					Plasma (ml./kg.)	Red Cells (ml./kg.)	Total (ml./kg.)	
E. P.	4	Febrile	68.2	47	48.5	43.1	91.6	2.3
	12	Diuretic	68.6	42	47.7	35.8	83.5	0.1
B. M.	4	Febrile	52.7	47	42.2	37.5	79.7	2.3
	12	Diuretic	48.4	36	47.5	27.0	74.0	7.7
A. M.	4	Febrile	70.0	45	44.9	36.8	81.7	5.8
	8	Diuretic	68.1	39	51.3	32.4	83.7	0.1
W. P.	3	Febrile	79.0	49	40.8	39.4	80.2	3.2
	8	Diuretic	78.6	42	47.2	34.4	81.6	0.1
	19	Convalescent	78.6	39	47.2	30.6	77.8	0.1

* Calculated on basis of initial weight except in the few instances in which the final weight was the greatest.
† Venous Wintrobe hematocrit corrected for 4 per cent trapped plasma.
‡ Died in shock.
§ These patients were in the hypotensive or "leakage" phase but did not have hypotension at the time of study.

group increased significantly, as demonstrated in Figure 1.

The red cell volume was decreased in four of the eight patients during the shock phase while the remainder had normal or slightly increased values. Large ecchymoses were present in both patients with low erythrocyte volumes although hemorrhage sufficient to account for such low values was not detected. Not only did the red cell volume of these two patients remain low during the subsequent phases and convalescence, but also those of three other patients decreased significantly in the subsequent phases. (Fig. 2.) The red cell volume in late convalescence among patients who had had a severe illness indicated a persistent anemia.

The changes in the total blood volume were almost as marked. Four patients showed total blood volumes less than normal during the shock phase, ranging from 45.7 to 70.2 ml./kg. body weight, while the remainder were within normal range. During the subsequent phases the total blood volumes tended to increase toward normal, as shown in Figure 3.

The plasma volume in one of the patients with moderately severe hemorrhagic fever was lower than normal during the hypotensive phase, while significant increases occurred in two others during later phases of the disease. The red cell volumes of two moderately ill patients decreased significantly during the period of renal insufficiency. The total blood volume was in the normal range in all patients of this group.

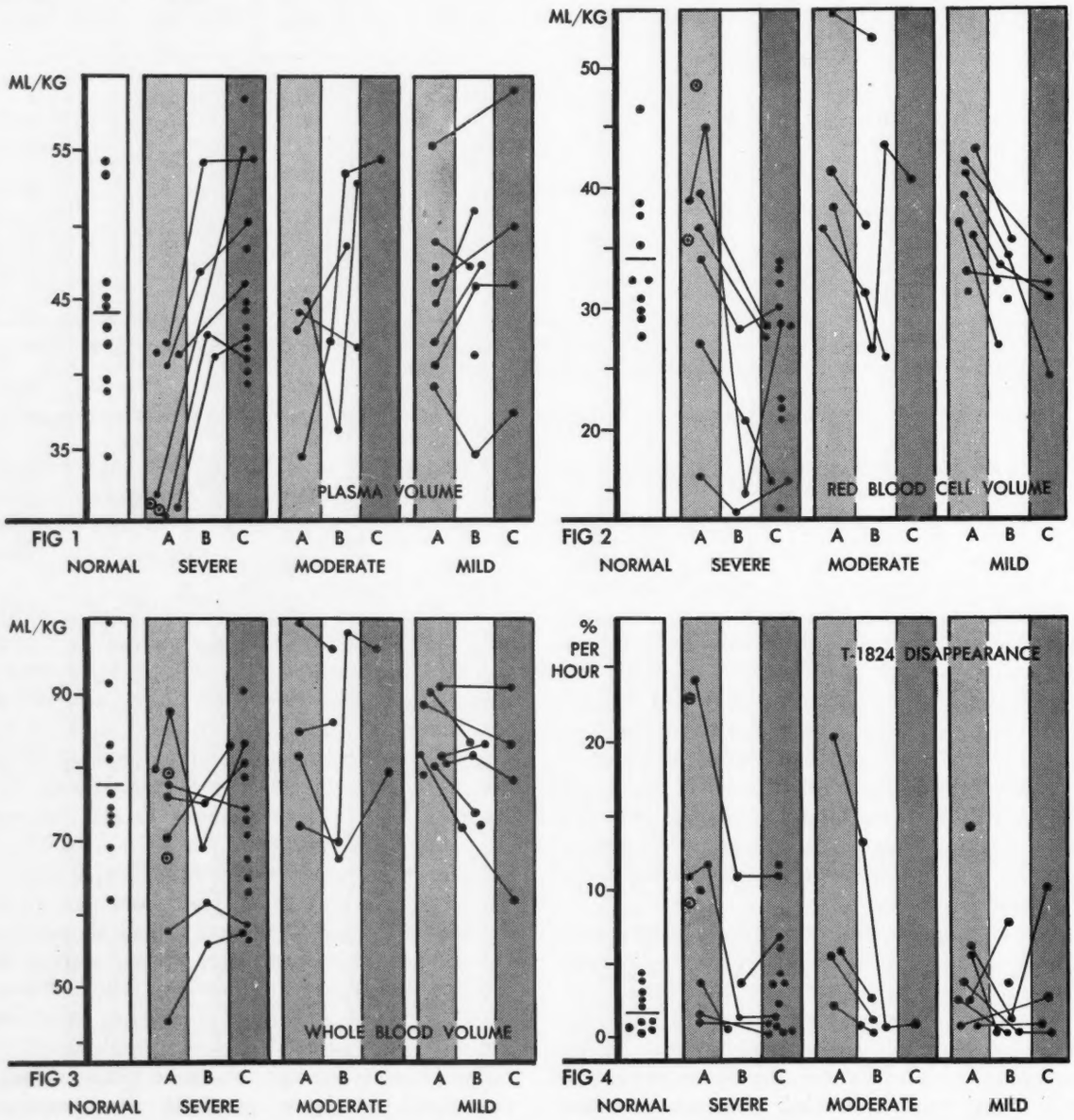
Changes in plasma and total blood volume in the mildly ill patients were less marked than in the other groups. However, a distinct tendency for the red cell volume to decrease was noted in the later stages. (Fig. 2.)

The Dye Disappearance Rate. The dye disappearance rate in the ten control studies ranged from 0.4 per cent to 4.4 per cent per hour, with a mean of 1.98 per cent $\pm$ 1.5. This compares to the mean of 5.2 $\pm$ 1.6 per cent reported by Gregersen.[15] During shock in hemorrhagic fever the disappearance rate was increased in the five patients with severe clinical shock, ranging from 9.4 to 24 per cent per hour. The three patients with milder shock had normal values, ranging from 1.0 to 3.1 per cent per hour. Among the moderately and mildly ill patients the disappearance rates were normal during the late febrile period in all but two, who had rates of 14 per cent and 20 per cent per hour. All values had returned to the normal range by convalescence, except in three patients who continued to have elevated disappearance rates during this period, with values ranging from 10 to 12 per cent. Two of these patients had had a severe course of illness.

Results with the P-32 Technic. Table II shows the total blood volume, red cell volume, and plasma volume in four normal individuals and in twelve patients during various phases of hemorrhagic fever, as determined by the radioactive phosphorus technic. Results in the normal individuals revealed a mean plasma volume of

39.1 ml./kg. body weight, a red cell volume of 32.1 ml./kg. and a total blood volume of 71.2 ml./kg., which agrees well with the results reported by others,[17] namely, 39.8, 25.8 and 65.6 ml./kg., respectively.

human albumin prior to the determination, showed a low red cell volume, a high normal plasma volume and a normal total blood volume. Five patients were studied during the late oliguric phase. All showed decreased red cell



FIGS. 1 to 4. Plasma, erythrocyte and whole blood volumes and T-1824 disappearance rates in severe, moderate and mild epidemic hemorrhagic fever. A, late febrile and hypotensive phases; B, oliguric and diuretic phases; C, convalescence; ⊙, patient died in shock.

Of the patients with hemorrhagic fever, one studied during the febrile phase showed a normal red cell volume and a decreased plasma and total blood volume. Determinations were made in three patients during shock. Two had reductions of all three values but the third patient, who had received one unit of concentrated

volume, low to low normal total blood volume, and low to normal plasma volume. Determinations in three patients during the diuretic phase revealed an increased total blood volume and plasma volume and decreased red cell volume in two, and normal values in the third. Studies in four convalescent patients, all with mild anemia,

demonstrated in each case a decreased red cell volume, normal or elevated plasma volume, and normal or low total blood volume.

Results of Simultaneous T-1824 and P-32 Blood Volume Measurements. It is unfortunate that more opportunity to make comparative studies between the T-1824 and P-32 technics was not available but the results in seven simultaneous determinations seemed to demonstrate identical trends. The body hematocrit was calculated from the formula:

$$\frac{\text{P-32 Red Cell Volume}}{\text{P-32 Red Cell Volume} + \text{T-1824 Plasma Volume}}$$

The ratio of the body hematocrit to the venous hematocrit (corrected for trapped plasma by the factor 0.96), together with the T-1824 plasma and P-32 red cell volume, is presented in Table III. It can be seen that this ratio was quite constant throughout the different phases of the disease in all but one of the patients (E. G.). That one discrepancy may represent a technical error. The mean and standard deviation of the ratios of six patients (excepting E. G.) is $0.84 \pm .04$.

TABLE II

P-32 BLOOD VOLUME DETERMINATIONS IN FOUR NORMAL SUBJECTS AND IN PATIENTS IN VARIOUS PHASES OF HEMORRHAGIC FEVER

Patient	Group	Weight (kg.)	Corrected Hematocrit*	Blood Volumes (ml./kg.)		
				Plasma	Red Cells	Total
E. L.	Normal	90.4	44	40.8	32.2	73.0
D. E.	Normal	69.0	46	37.8	32.5	70.3
T. D.	Normal	63.6	49	36.2	34.2	70.4
J. B.	Normal	70.5	42	41.8	29.8	71.6
D. D.	Febrile	81.8	54	28.6	33.9	62.5
P. T.†	Shock	75.9	53	23.2	26.2	49.4
E. A.	Shock	65.0	39	43.5	28.3	71.8
H. S.†	Shock	76.4	48	31.2	28.2	59.4
V. R. C.	Oliguric	56.8	39	29.0	18.9	47.9
D. K.	Oliguric	65.0	45	27.8	22.8	50.6
C. W.	Oliguric	73.1	43	38.8	29.2	68
K. N.	Oliguric	71.8	43	32.0	24.1	56.1
E. S.	Oliguric	62.6	42	39.8	28.5	68.3
J. T. P.	Diuretic	54.5	45	39.1	32.2	71.3
E. G.†	Diuretic	74.1	25	67.8	22.4	90.2
H. P.	Diuretic	55.5	40	46.4	31.9	78.3
E. B.	Convalescent	58.6	35	44.7	24.0	68.7
A. C.†	Convalescent	71.4	37	39.5	22.4	61.9
V. R. C.†	Convalescent	57.2	36	47.0	25.2	72.2
M. M.	Convalescent	73.1	44	36.2	28.6	64.8

* Venous Wintrobe hematocrit corrected for 4 per cent trapped plasma.

† These patients also appear in Table I.

COMMENTS

Any attempt to make a correlation between blood volume reduction and shock in cases of hemorrhagic fever is made difficult by the fact that control determinations of blood volume before the illness are not available. An estimate of the loss of volume, however, may be made by: (1) comparison of the volume during shock with that during recovery; and (2) comparison of the value during shock with the average normal value. The latter method, however, may be misleading since the range of normal values is so wide. Although the changes in blood volume demonstrated in this study by comparison with the average normal were marked in some cases, the changes demonstrated by serial determinations in individual patients were more impressive.

TABLE III

RESULTS OF SIMULTANEOUS T-1824 AND P-32 BLOOD VOLUME DETERMINATIONS IN HEMORRHAGIC FEVER

Patient	Phase of Disease	Corrected Hematocrit*	T-1824 Plasma Volume (ml.)	P-32 Red Cell Volume (ml.)	Body Hct. / Venous Hct.
D. E.	Normal	46	3800	2240	0.81
P. T.	Shock	54	2350	2020	0.86
H. S.	Shock	47	3140	2130	0.86
E. G.	Diuretic	25	3200	1760	1.37
H. P.	Diuretic	40	3180	1770	0.88
V. R. C.	Convalescent	35	3400	1440	0.86
A. C.	Convalescent	36	4150	1570	0.77

* Venous Wintrobe hematocrit corrected for 4 per cent trapped plasma.

That patients with severe infections go into shock has been well known for years. This occurs most commonly during defervescence, when there may be widespread cutaneous vasodilation. Ebert and Stead,[2] in their studies of the blood volume of patients with severe infections, for the most part pneumococcus pneumonia accompanied by shock, found the blood volume to be normal or only slightly reduced. Aub, Zamecnik and Nathanson,[3] working with dogs given Clostridium oedematiens toxin, noted that plasma volume did not decline until late in the course of the experiment. Both groups of workers deduced that the primary cause of shock in these instances was vasodilatation.

The majority of the patients with mild degrees of hemorrhagic fever defervesce without clinically significant change in blood pressure or hematocrit and proceed directly into the phase of renal insufficiency. As was expected, the plasma volume and dye disappearance in such patients were usually within the normal range. Some of the patients in whom shock developed, however, had a decreased plasma volume and increased

T-1824 disappearance rate. The plasma volume during shock was usually lower and the dye disappearance rate higher than in other groups and phases. When the figures for plasma volume of the shock patients are examined individually, however, the decrease is noted to be most obvious in those patients who had severe shock, and only slightly decreased in the milder cases. The extremely high hematocrits observed during severe shock in hemorrhagic fever and the massive retroperitoneal edema observed postmortem in patients dying from shock is therefore in all probability due to plasma leakage.*

Total blood volume was reduced in six patients during shock (four by the T-1824 technic and two by the P-32 technic). In these patients the total blood volume ranged between 12 and 41 per cent below normal. Emerson and Ebert[18] found that in traumatic shock with hemorrhage, blood volumes reduced by more than 25 per cent of the predicted normal were almost uniformly accompanied by systolic arterial pressures below 85 mm. Hg. A reduction of total blood volume caused by loss of plasma, however, is probably not the sole cause of shock in hemorrhagic fever, for the T-1824 total blood volume of four patients in clinical shock was within the normal range.

Shock appears so suddenly in hemorrhagic fever that there was little opportunity to study the rapidity with which capillary leakage occurred and with which plasma volume decreased. Patient V. R. (Table 1), however, had identical disappearance rates and plasma volumes on the day before and on the day of shock, an indication that active capillary leakage occurred at least twenty-four hours before clinical shock. The lack of any significant change in whole blood volume during this period indicated that a mechanism other than change in blood volume was involved in the immediate cause of shock.

Little change in the red cell volume was noted during the shock phase in the majority of patients. However, during severe shock a marked reduction in the T-1824 red cell volume of two patients was noted which persisted into convalescence. All of the P-32 red cell volumes during this phase were slightly reduced as well. The decrease in circulating red cell mass was far beyond that which could be accounted for by hemorrhage; and as there was no clinical or laboratory evidence of jaundice, it is not likely that hemolysis contributed to the acute reduction. A more plausible explanation is the trapping of red cells in the dilated capillaries, a phenomenon seen in histologic preparations of a number of organs.[19]

Despite a definite return of plasma volume toward normal at the end of the hypotensive phase (Fig. 1), the red cell volume exhibited a tendency toward further decrease (Fig. 2) which often persisted into convalescence.

Noble and Gregersen,[20] in studying patients with shock due to hemorrhage, skeletal trauma and burns, found that the T-1824 disappearance rate was significantly increased only in the burn patients. The dye disappearance rate in some patients with hemorrhagic fever was increased to the same order of magnitude as that observed in severe burns. This increase generally occurred during the late febrile and shock phases when the capillary leakage appeared to be at a maximum. In addition, T-1824 administered at this time accumulated in retroperitoneal edema and also was excreted in the urine in amounts sufficient to color it a blue-green.

Although the simultaneous P-32 and T-1824 blood volume determinations were few in number, the ratio of the body hematocrit to the venous hematocrit was the same in six of the seven studies despite differences in the phase of the disease and wide differences in venous hematocrits. The single discrepancy could represent a technical error, the effect of marked fluid shifts during the diuretic phase of the disease or the continued trapping of large numbers of erythrocytes in dilated capillaries. Further observations are needed to clarify this matter. The mean of the ratio of body hematocrit to venous hematocrit in the six determinations (excepting E. G.) is $0.84 \pm .04$, which does not differ markedly from those reported by other authors.[16,21,22]

CONCLUSIONS

1. Plasma T-1824 disappearance rates and blood volumes by the T-1824 and P-32 technics were determined serially in a number of patients with hemorrhagic fever.

2. Patients in severe shock exhibited increased T-1824 disappearance rates and decreased plasma volumes and total blood volumes.

3. The disappearance rates in patients with mild or no shock were usually only slightly in-

* Patient P. C. died in shock twelve hours after T-1824 had been given intravenously. At necropsy the retroperitoneal edema fluid was blue-tinged, which further supports the theory of plasma leakage.

creased, while their plasma volumes were in the low normal range and the total blood volumes were normal.

4. These observations suggest that a mechanism other than decrease in total blood volume is the primary cause of shock in hemorrhagic fever. A significant decrease of blood volume also occurs, however, and must contribute significantly to the severity of the shock.

5. Plasma volume rapidly returned to normal at the end of the hypotensive phase.

6. Although most patients showed low normal to normal red cell volumes during the febrile and shock phase of the disease, two showed a significant decrease during severe shock and many others had decreases in later phases. The cause of this may be trapping of red cells in the dilated capillary bed. This persisted into convalescence in patients who had been severely ill.

7. T-1824 and P-32 technics for measuring blood volumes yielded similar results in all phases of hemorrhagic fever.

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Relation between Hematocrit and Total Serum Proteins in Epidemic Hemorrhagic Fever*

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THE hematocrit, one of the most useful guides to the clinical evaluation and management of patients with hemorrhagic fever, frequently begins to increase during the late febrile phase of hemorrhagic fever and reaches a maximum during the hypotensive phase. It then rather abruptly decreases as the patient goes from the hypotensive phase into the oliguric period. The degree of increase in hematocrit is roughly correlated with the severity of hypotension or shock but may occur even when there is no hypotension.[1] Further, protein-rich retroperitoneal edema is found at autopsy in patients who died at or near the time of the maximum hematocrit.[2] Finally, the increase in hematocrit occurs at a time when plasma volume is reduced.[3] For these reasons the hematocrit in hemorrhagic fever is considered to reflect chiefly the loss of plasma from the vascular system and its subsequent return. If this be the case, the changing hematocrit should *not* be accompanied by parallel changes in the total serum protein.

The hematocrit was routinely measured by the specific gravity technic§[6] during the fall 1952 outbreak of hemorrhagic fever. Total serum protein values obtained during these measurements were recorded on the charts of twelve patients during the febrile, hypotensive and early "recovery" phases. These data, shown in Figure 1, indicate a considerably greater increase of

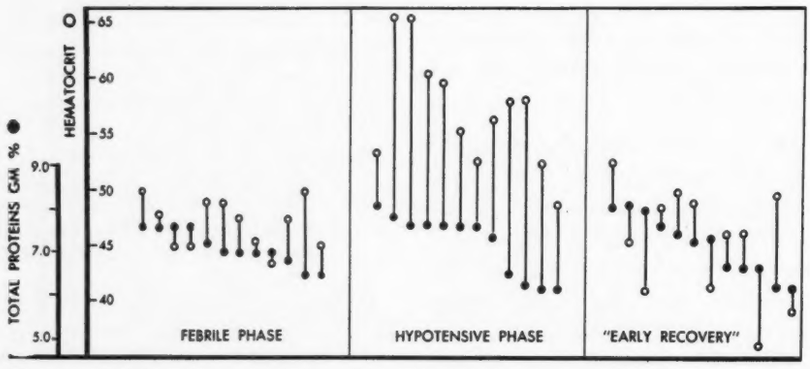

FIG. 1. Relation between hematocrit and total serum protein during the early phases of hemorrhagic fever in twelve patients. "Early Recovery" refers to first reasonably stable hematocrit after decrease from maximum value observed during hypotensive phase.

§ Concerning the accuracy of the hematocrit determinations in hemorrhagic fever, good agreement between the specific gravity and Wintrobe methods was noted[4] when the hematocrit was less than 55, but above this value the Wintrobe technic yielded higher results. During the course of another study[5] good agreement between arterial and venous hematocrits was observed in all phases of hemorrhagic fever.

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hematocrit than of the total serum proteins at the height of the hypotensive phase. This represents loss of plasma in excess of erythrocytes from effective circulation. The early "recovery" values were selected on the basis of the initial reasonably stable hematocrit after its decrease from the maximum during the hypotensive phase. These figures, when compared to the hypotensive phase values, reflect the return of sequestered plasma to effective circulation. A modest increase in total serum protein value in several patients during the hypotensive and early "recovery" periods probably reflects some degree of dehydration, which is not uncommon toward the end of the hypotensive phase.

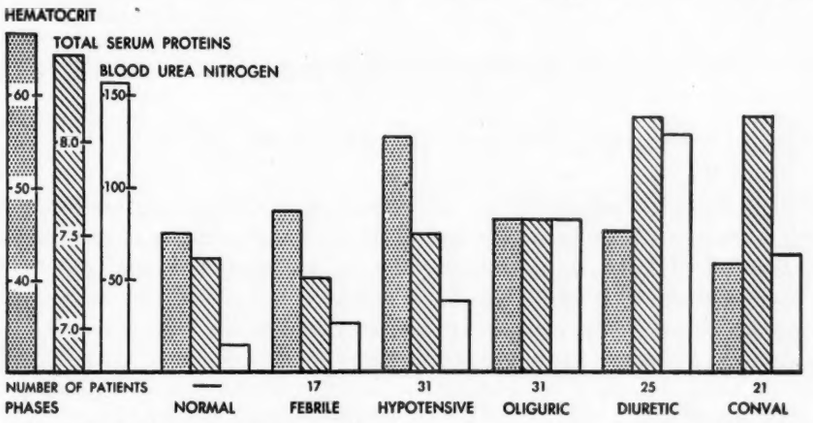

FIG. 2. Serial changes in hematocrit, total serum proteins and blood urea nitrogen throughout all phases of hemorrhagic fever.

The average values for hematocrit, total serum proteins and blood urea nitrogen for all patients who had simultaneous measurements of these items recorded throughout three or more phases are shown in Figure 2. Note the considerable increase in total proteins during the diuretic phase which persists into convalescence. This may in part be due to dehydration which is not reflected by a similar increase in hematocrit since many patients have some degree of anemia. However, an electrophoretic study of the serum proteins in hemorrhagic fever[7] has shown that the serum albumin falls below normal from the hypotensive phase into convalescence, and that some of the globulin fractions are increased. Moreover, the specific gravity methods yield falsely high total protein values in the presence of significant retention of non-protein nitrogenous materials. This may account for some of the apparent increase in serum proteins during the oliguric and early diuretic phase, but it will be noted in Figure 2 that the proteins remained at high levels during early convalescence despite a marked decrease in blood urea nitrogen.

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Plethysmographic Studies in Epidemic Hemorrhagic Fever*

Preliminary Observations

LIEUT. WILLIAM W. MCCLURE, M.C.†

AMONG the physiologic investigations of epidemic hemorrhagic fever conducted during the fall of 1952, a plethysmographic study was instituted to establish the nature of the vascular injury. This report summarizes the results of twenty separate records obtained from seven hemorrhagic fever patients in varying stages of the illness.

METHODS

The plethysmograph† employed was the portable pneumatic model of Burch and Winsor.[1,2] An air-conditioned, constant temperature environment was not available and all observations were made either at the patient's bedside or in a corner of an open ward reserved for the purpose. The usual range in temperature was 22 to 25°C.

Observations were made with the patient lying as comfortably as possible in bed, covered according to his wishes, usually with a sheet and one blanket. In all instances the fingers were normally warm to touch. Some patients were seriously ill, restless and febrile, and comfort could not be achieved. Psychic stimuli were avoided where possible, though the clangor from a busy hospital routine was unavoidable. When the effect of drugs on the tracings was studied, solutions were administered intravenously through a previously placed needle and three-way stopcock, to minimize the effect of pain.

All measurements were made upon the left index fingertip, using standard technics.[2–4] Digital blood flows were determined by the venous occlusion method.[4] Before each experiment the sensitivity of the recording instrument was calibrated according to the volume of fingertip enclosed in the chamber, so that recorded volume changes were expressed in cubic millimeters per 5 ml. of tissue. Recordings were analyzed and are described in terms used by Burch, Cohn and Neumann.[3]

In eleven instances "reactive hyperemia" was studied. Arterial occlusion was accomplished by means of an upper arm cuff inflated approximately 20 mm. Hg above a systolic pressure for ten minutes. Following release of the arterial occlusion, blood flows were determined at intervals until a peak and subsequent decline in flow were noted.

As the vascular lesions of hemorrhagic fever are thought to be associated at certain times with an abnormal loss of plasma from the blood vessels into the tissues,[5,6] a method was employed to study the change in finger volume following venous occlusion of standard duration. A control observation was made for five to ten minutes. During this time the baseline was so adjusted that the string shadow returned approximately to the center of the paper after the excursions of the larger amplitude waves had subsided. The baseline was then left in this position for at least three minutes before venous occlusion was started. A standard pressure of 60 mm. Hg of five minutes' duration was employed, using the finger cuff. In all cases finger volume increased during occlusion and fell after release. The string was allowed to stabilize after release of the occlusion. The baseline was then adjusted as necessary to return the string to its original position, and the record continued for five

† Manufactured by the Cambridge Instrument Company, Inc., New York, N. Y.

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minutes. The resultant change in baseline was calculated in terms of cubic millimeters of persistent change in volume per 5 ml. of tissue. In all cases environmental temperature was checked with a laboratory thermometer placed within a few inches of the finger cup. If during the period of observation the air temperature varied more than 0.5°C., the quantitative measurements of volume changes were considered erroneous and were discarded.

Although spontaneous changes in volume occurred constantly and might be of considerable magnitude (particularly the beta wave), the technic employed made it possible to distinguish without difficulty spontaneous variations from those produced by the venous occlusion. It was assumed that this persistent change in volume following the release of venous occlusion was related to fluid shifts between the blood vessels and tissues of the finger, and would therefore reflect to some extent the integrity of capillary walls. The true significance of observations made with this technic in hemorrhagic fever is not certain, however, and must be determined by further study.

In six patients the effect of L-arterenol was studied. The drug was administered by continuous intravenous drip and regulated by means of a modified tunnel clamp to a rate sufficient to maintain the systolic pressure between 110 and 130 mm. Hg.

TABLE 1

SUMMARY OF TWENTY PLETHYSMOGRAPHIC OBSERVATIONS IN SEVEN PATIENTS WITH EPIDEMIC HEMORRHAGIC FEVER

Patient	Day of Disease	Oral Temperature	Blood Pressure*	Pulse Wave (cu. mm.)		Respiratory Wave (Present + Absent 0)	Alpha Wave		Beta Wave		Resting Blood Flow (cu. mm./5 ml./second)			Flow after 10 Arterial Occlusion (cu. mm./5 ml./second)			Volume Change After 5 Venous Occlusion	
				Maximum	Minimum		Cu. mm.	Cycles/Minute	Cu. mm.	Cycles/Minute	Maximum	Minimum	Average	Maximum	Minimum	Average	Cu. mm.	Per cent†
W. R.	7	98.0	108/70	9.0	1.0	0	7	2.0	29.0	1.5	25.0	7.0	18.0	....	....	....	32.5	0.7
	38	98.8	128/68	5.5	1.0	0	11	4.0	40+	1.0	52.0	46.0	48.7	....	....	....	−25.0	−0.5
J. D.	7	98.0	128/74	3.0	0.5	0	13	4.0	0.0	0.0	6.5	3.5	5.0	4.8	1.5	3.6	100.0	2.0
	16	98.4	132/74	7.0	1.5	0	10	2.4	20.0	0.6	22.5	13.0	19.1	26.0	20.0	22.7	−45.0	−0.9
R. M.	6	99.8	106/64	7.0	1.5	+	19	3.0	33.5	0.7	22.5	11.0	15.9	58.0	22.0	36.3	105.0	2.1
	11	97.8	118/74	11.5	1.0	+	13	6.0	41.0	2.0	34.0	12.5	24.3	23.0	11.0	17.0	0.0	0.0
S. M.	3	99.4	88/48	3.0	1.0	0	8	2.0	39.0	1.0	6.5	5.0	5.4	12.0	2.0	5.3	0.0	0.0
	4‡	99.4	118/92	2.0	1.0	+	0	0.0	0.0	0.0	17.0	5.0	10.3	9.0	3.0	6.6	0.0	0.0
	30	?	?	1.0	0.5	0	0	0.0	0.0	0.0	....	....	....	....	....	....	27.0	0.5
	39	.....	.....	....	....	..	..	...	....	....	84.0	26.0	44.0	....	....	....	.....	.....
P. O.	3	104.4	110/86	2.5	1.0	0	12	5.0	50.0	1.0	57.0	35.0	47.0	27.0	9.0	16.0	232.0	4.6
	3‡	.....	.....	3.0	1.5	0	20	2.8	30.0	1.0	44.0	16.0	31.2	38.0	20.0	30.7	115.0	2.3
	6‡	98.0	128/94	2.0	0.2	0	16	4.0	24.0	0.35	30.0	16.0	21.8	16.0	6.5	10.7	55.0	1.1
L. A.	2	102.4	122/76	7.0	2.0	0	25	3.5	45.0	1.0	6.0	4.0	5.1	11.0	4.0	6.9	0.0	0.0
	6§	98.2	112/70	12.0	10.0	0	12	3.0	40+	0.8	34.0	17.0	18.9	35.0	10.0	21.0	87.5	1.8
R. K.	2	104.4	98/40	5.0	4.0	+	13	4.0	0.0	0.0	7.0	5.0	5.7	....	....	....	0.0	0.0
	2‡	.....	.....	4.0	2.0	0	5	4.0	0.0	0.0	....	....	....	....	....	....	0.0	0.0
	4‡	102.4	110/76	11.0	5.0	+	13	2.0	45.0	1.0	....	....	....	....	....	....	20.0	0.4
	4‡	.....	.....	8.5	3.0	+	29	5.0	52.0	2.0	48.0	36.0	42.9	....	....	....	68.75	1.4
	26	99.0	125/84	4.0	3.0	0	8	4.0	30.0	0.2	16.0	16.0	16.0	....	....	....	−24.0	−0.5

* Brachial artery pressure as measured with a sphygmomanometer cuff.
† Change in volume expressed as per cent of 5 ml. fingertip volume.
‡ During the administration of L-arterenol.
§ Received L-arterenol for three days prior to study; now off medication.

RESULTS

The observations are summarized in Table 1. All waves described as occurring in the normal plethysmogram were seen. No consistent abnormal pattern was evident for the pulse, respiratory, alpha, beta or gamma waves.

Pulse wave volume showed no correlation with fever, day of illness or brachial arterial pressure. Within each individual record there were often great changes in the magnitude of pulse tracings. No attempt was made to study the contour of the waves.

Resting blood flow was highly variable among individuals as well as in the group as a whole. There was no consistent correlation between blood flow and oral temperature or day of illness.* Average resting flow was highest (48.7

* See Addendum for results of subsequent observations.

cu. mm/5 ml./second) in patient W. R. on the thirty-eighth day of illness with normal oral temperature. Lower flows were frequently seen in patients with fever.

Response of blood flow to a ten-minute arterial occlusion (reactive hyperemia) was studied in eleven instances. On seven occasions no appreciable increase in blood flow occurred,* as compared with the maximum flow obtained during the control period. This failure of response could not be traced to the technic employed.

Persistent volume change of the finger after a standard venous occlusion was tested on nineteen occasions. Changes ranged from a decrease in volume of 0.9 per cent to an increase of 4.6 per cent. Increases in volume greater than 1 per cent (50 cu. mm.) were considered significant. Significant volume increases occurred on seven occasions in five patients between the third and seventh days of illness, the period during which there is the greatest clinical evidence of vascular damage and instability.[5,6] Four records taken on three patients during this stage of the illness showed no significant change in volume. Of these, two records were made during the continuous intravenous administration of L-arterenol.

No consistent effect of L-arterenol on the plethysmogram could be seen.* Occasionally a damping effect was noted in a previously labile tracing immediately after administration of the drug was started. In general, after several hours of continuous infusion of the drug the tracings could not be distinguished from those of patients who received no drug. No depression of blood flow was noted after prolonged infusion. From the data on hand no statement can be made regarding the effect of L-arterenol on the persistent volume change following the release of standard venous occlusion. Preliminary evidence suggests that the drug may have some inhibitory effect on such volume changes.

COMMENTS

The plethysmographic method is subject to many variables which may influence the final recordings. In this study as much care as possible was taken to avoid breaches in technic but the experimental conditions were not ideal. Even under the most favorable circumstances the range of variation of normal tracings is so great that interpretation in the presence of borderline or moderate vascular disease may be difficult or impossible. The number of observations in this report, moreover, is insufficient for valid statistical analysis and definite conclusions cannot be drawn from this study.

Of the observations reported here, perhaps the most important are negative in nature. No clear-cut difference is evident between the plethysmographic waves seen in this disease and those of normal individuals. In some instances there seemed to be a general increase in lability of the tracings but this was not a constant finding and could not be correlated with other phenomena.

No explanation can be found for the absence of reactive hyperemia following release of a ten-minute arterial occlusion, as was observed on seven occasions among eleven experiments. Six of the negative results were obtained in patients between the third and seventh days of illness, when clinical evidence of vascular disturbance is most noticeable. This failure of response may be the result of maximal dilatation during the control period or inability of the vessels to respond to anoxia with an increase in blood flow. Three patients of this group had fever at the time of observation.

SUMMARY AND CONCLUSIONS

1. Twenty separate plethysmographic observations on seven patients in varying stages of hemorrhagic fever are presented. All studies were made upon the fingertip. Standard technics were employed, with the exception that environmental conditions could not be ideally controlled.

2. Spontaneous variations in finger volume were characterized by the appearance of all waves commonly described as present in the normal individual. No distinct difference between the pattern in hemorrhagic fever and that of normal tracings was seen.

3. Blood flow determined by the venous occlusion method was highly variable and showed no consistent relationship to the stage of illness or the oral temperature.

4. Reactive hyperemia following a ten-minute arterial occlusion was tested on eleven occasions. In seven instances no increase in flow over maximum control values was seen. No explanation for this failure of reactive hyperemia has been found.

5. Significant volume increases after venous occlusion were noted on seven occasions in patients during the third to seventh days of illness,

* See Addendum for results of subsequent observations.

the period when the greatest clinical evidence of vascular abnormality is seen. These persistent volume increases appear to be related to the period of the disease when loss of plasma through damaged capillaries occurs.

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Addendum: More extensive plethysmographic observations, as yet unpublished, were made by Dr. Richard Lyons during the fall 1953 outbreak of hemorrhagic fever. These studies demonstrated a marked increase in peripheral blood flow during the "hyperdynamic" or "hypervolemic" phase; a reactive hyperemia in response to arterial occlusion in the majority of patients studied; and usually reduced peripheral blood flow after rapid administration of L-arterenol.

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Cardiac Output in Epidemic Hemorrhagic Fever*

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A SURVEY of changes in cardiac output during the various phases of hemorrhagic fever was initiated during the fall of 1952. Fifteen observations were made but the epidemic terminated before an adequate number of studies could be obtained in each phase of the disease. Nevertheless, the data available suggest a different pattern in each of several phases of the disease and are presented here as a preliminary report.

METHODS

The cardiac output was measured by the Hamilton technic.[1] The dye was injected as rapidly as possible into an antecubital vein. Blood samples were obtained every two to three seconds through a Cournand needle placed in a femoral artery. Several observations on patients in shock were discarded because the dye time-concentration curve did not exhibit a sharp peaked configuration. Duplicate determinations were made at half hour intervals in four patients and differed by less than 0.4 L. per minute in three. In the fourth patient the two measurements differed by 0.9 L. per minute. Venous pressure was measured with a saline manometer connected to a needle placed in an antecubital vein. The xiphoid served as the zero reference point. Mean femoral arterial pressure was measured on a damped, aneroid manometer attached directly to the arterial needle. Peripheral resistance, expressed in arbitrary units, was calculated by dividing the difference between mean arterial and venous pressure by cardiac output.

RESULTS

The results are summarized in Table 1. As might be expected, the cardiac index was increased while peripheral resistance was reduced during the *febrile* phase.

During the *hypotensive* phase, within twenty-four hours of the maximum hematocrit, the cardiac index was near or below the lower limits of normal despite the fact that two of the four patients were still febrile. None of the subjects were in clinical shock at the time of study, although patient 8 had received 1 unit of serum albumin fifteen minutes earlier because of hypotension and shock. Peripheral resistance was not increased in the hypotensive phase.

Three patients were studied in the early *oliguric* phase. Their hematocrits had been decreasing for twenty-four hours at the time of study, a reflection of the return of sequestered plasma to effective circulation.[2] In these subjects the cardiac index was in the normal range while peripheral resistance was still at or slightly below the normal limits.

Four observations were made in patients who had clinical evidence of the *hypervolemic* syndrome.[2] Hypertension was present in three, and all had distended veins. Despite this the venous pressure was normal, as it was in all of the studies listed in Table 1. The cardiac index was well above normal and peripheral resistance was decreased in two of the patients while cardiac index was normal; but peripheral resistance was increased in the other two, one of whom had had a 500 ml. phlebotomy twenty-four hours prior to study.

COMMENT

Although the data presented are limited in number, the reduced blood volume characteristic of the hypotensive phase of hemorrhagic fever appears to be associated with some decrease in cardiac index. Unlike other situations in which blood volume is decreased, peripheral resistance is not increased during the hypotensive phase of

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TABLE I

HEMODYNAMIC OBSERVATIONS IN HEMORRHAGIC FEVER

Patient	Day of Illness	Temperature, Hematocrit		Mean Arterial Blood Pressure (mm. Hg)	Venous Pressure (mm. saline)	Cardiac Index (L./Min./m²)	Peripheral Resistance* (Units)	T-1824 Circulation Time (Secs.)
		(°F.)	(% Red Blood Cells)					
Normal	..	....	45	90–105	100	3–4	15–20	15
Febrile Phase—Early Hematocrit Increase								
1	2	103.8	50	86	65	5.0	8.0	10
2	2	103	49	87	65	4.0	10.5	7
3	2	101	52	76	70	8.0	4.5	25
4	3	102	51	76	25	4.6	9.1	12
Hypotensive Phase—Mid-hematocrit Increase								
5	3	101	55	88	53	2.3	17.7	24
6	4	98.6	56	102	54	2.7	18.5	12
7	4	102.6	51	70	3	3.3	12.0	20
8†	5	98.6	54	81	94	3.2	12.0	15
Oliguric Phase—Early "Recovery"—Hematocrit Decreasing								
9	4	100	46	90	15	3.6	11.8	17
2	6	100	51	98	24	3.8	12.5	12
10	7	98.6	50	92	36	3.2	14.6	16
Oliguric and Diuretic Phases—"Hypervolemic Syndrome"								
11	8	98.6	45	87	45	4.6	12.3	13
12‡	9	98.8	36	124	40	3.0	24.0	12
13	9	98.6	47	110	..	3.8	28.9	..
7	10	100	40.	120	60	6.8	7.0	10

* (Mean arterial pressure-venous pressure) ÷ cardiac output.
† Given 1 unit serum albumin for shock just prior to study.
‡ Phlebotomy twenty-four hours prior to study.

hemorrhagic fever. This suggests that arteriolar dysfunction is also present during this phase of hemorrhagic fever. Limited observations during later phases of hemorrhagic fever suggest that increased cardiac output and decreased peripheral resistance may be present during hypertension and the "hypervolemic" or "hyperdynamic" syndrome.*

* More extensive but as yet unpublished observations were made on cardiac output and peripheral resistance during the fall 1953 outbreak of hemorrhagic fever by Lieut. G. Entwisle. A number of patients were studied during clinical shock and three were studied during the "hypervolemic" syndrome. These data confirm the preliminary observations contained in the present report.

SUMMARY

1. The cardiac index is increased during the febrile phase and hypervolemic syndrome in hemorrhagic fever and is decreased or low normal during the hypotensive phase.

2. Peripheral resistance is generally decreased in all phases of hemorrhagic fever except during the hypotensive phase when it is normal.

3. The venous pressure is normal in all phases of hemorrhagic fever, including the hypervolemic syndrome.

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Renal Function in Epidemic Hemorrhagic Fever*

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THE clinical diagnosis of epidemic hemorrhagic fever depends on the appearance of proteinuria along with certain clinical manifestations as discussed in other papers of this symposium. Azotemia, oliguria, isosthenuria or hyposthenuria, microscopic and gross hematuria, and cylindruria are common indications of renal involvement throughout the course of the disease.

At autopsy the kidneys are swollen and show intense congestion in the renal medulla with diapedesis of red cells. The glomeruli appear relatively normal although proteinuric deposits in Bowman's capsule reflect increased capillary permeability. Casts in the convoluted tubules and patchy degeneration of tubular epithelium are likewise not infrequently seen. Sometimes a peculiar bland necrosis of the center of the pyramids appears.[1,2]

The mechanism by which renal damage is produced in hemorrhagic fever is not known. This study was undertaken in an attempt to define renal hemodynamic alterations in this disease.

MATERIALS AND METHODS

The present paper describes serial observations of renal hemodynamics made in eight young servicemen with hemorrhagic fever during the fall 1952 outbreak. Two patients (E. H. and W. P.) had mild illness, five (F. R., J. T., S. M., P. O. and L. A.) were moderately ill and one (V. R.-C.) was severely ill. There were no deaths in this group.

During the fall 1952 outbreak selected patients were treated with constant intravenous infusions of L-arterenol[3] from the febrile phase (first to about the fifth day of disease) through the "leakage" or "shock" phase (fourth to seventh day) of their disease. It was hoped that prevention of abnormal vasodilatation and maintenance of normal arterial pressure through this critical period might minimize renal damage. Two (L. A. and P. O.) of the eight patients were in this group. Two other patients (V. R.-C. and S. M.) received L-arterenol infusions in treatment of shock. The remaining four patients did not develop shock and received no L-arterenol.

As estimates of glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), inulin and para-aminohippurate clearances (C_{IN} and C_{PAH}) were measured by standard technics.[4] The test substances were administered by constant intravenous infusion following a priming dose. A tunnel clamp made from tongue depressors and screw clamps permitted satisfactory control of the infusion rate. Working plasma levels of inulin were usually 18 to 25 mg. per cent and of PAH, 1 to 2.5 mg. per cent. However, in the presence of severe azotemia lower plasma levels of PAH (0.5 to 1.0 mg. per cent) were used in an effort to maintain renal extraction of PAH at a maximum. After each urine collection the bladder was washed two or three times with a total of 60 to 90 ml. saline, followed by air.

A constant temperature bath was improvised permitting relatively simple analysis of inulin by the resorcinol method.[5] Inulin recoveries varied from 96 to 101 per cent and PAH from 98 to 101 per cent for urine and plasma. Serum blanks for inulin and PAH were obtained and inulinoid blanks were measured in timed urine specimens in each experiment.

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With the exception of one study during shock (V. R.-C.), the values reported are averages of three or four clearance periods of approximately twenty minutes each. No correction for weight or surface area has been made. No effort was made to induce water diuresis prior to clearance studies because the water loading of these patients was contraindicated clinically. J. T. is the only exception and this study was performed on his thirty-second day of illness.

TABLE I

RENAL FUNCTION IN EPIDEMIC HEMORRHAGIC FEVER

Patient	Phase of Disease	Day of Disease	Maximum Temp. (F.)	Hematocrit (%)	Proteinuria	Urine Volume (ml./day)	Urine Specific Gravity	Blood Urea N.	C_{IN} (ml./min.)	C_{PAH} (ml./min.)	Filtration Fraction	ERBF (ml./min.)	Urine Flow (ml./min.)	Remarks
	Febrile	3	102.8	49	0	890	1.030	16	130	857	0.152	1694	0.72	No shock or oliguria; highest
E. H.	Diuretic	5	99.6	45	4+	2520	1.008	19	120	748	0.162	1383	1.52	BUN 19 mg. % on 5th day
	Conval.	11	97.0	46	0	1890	1.010	14	115	641	0.180	1194	1.44	
	Febrile	4	102.2	51	0	805	1.024	...	136	745	0.179	1521	0.67	No shock or oliguria
W. P.	Diuretic	6	98.4	50	3+	3120	1.008	21	89	379	0.237	758	2.33	
	Conval.	9	98.6	45	0	....	1.010	...	126	569	0.227	1034	3.54	
	Febrile	4	103.0	49	4+	740	1.024	16	136	647	0.211	1268	0.65	No shock; highest BUN 56 mg.
F. R.	Oliguric	7	99.4	47	4+	....	1.010	31	19	130	0.151	245	0.62	% on 9th day
	Diuretic	9	99.2	41	1+	2200	1.003	56	19	74	0.256	125	1.58	
	Conval.	17	.....	43	0	....	.....	11	100	470	0.213	822	3.17	
	Febrile	4	104.0	48	1+	500	1.015	16	160	900	0.176	1774	2.03	Required Trendelenburg posi-
J. T.	Oliguric	6	99.4	48	4+	850	1.018	38	36	222	0.165	426	1.05	tion part of 6th day; highest
	Oliguric	8	97.6	34	4+	330	1.012	70	9	100	0.087	152	0.66	BUN 99 mg. % on 10th day
	Diuretic	13	.....	30	0	3800	1.006	61	58	297	0.198	424	2.37	Tm_{PAH} 118 mg./min.
	Conval.	32	.....	39	0	....	1.016	...	115	574	0.200	941	9.26	
	Febrile	4	104.0	50	1+	1450	1.024	18	145	826	0.181	1648	0.95	Shock required L-arterenol for
	Shock	5	105.4	56	3+	540	1.025	23	88	431	0.204	980	1.03	3 days. 50 gm. albumin on 6th
									49	260	0.187	590	0.26	day; oliguric 5th, 6th and 7th
V. R.-C.									95*	552	0.172	1250	0.94	days; highest BUN 152 mg. %
	Diuretic	11	99.0	35	3+	5130	1.010	121	20	136	0.150	210	3.93	on 9th day
	Diuretic	16	98.6	32	0	3700	1.006	46	59	299	0.199	443	3.33	
	Conval.	44	.....	42	0	....	1.012	...	90	500	0.180	862	....	
	Shock	4	98.6	59	4+	300	.....	72	18	192	0.092	469	0.60	Treated with albumin for shock
									22*	182	0.122	444	0.65	at forward hosp.; L-arterenol
S. M.	Diuretic	11	98.6	43	2+	4370	1.008	84	46	231	0.199	403	2.61	4th to 6th days; highest BUN
	Conval.	29	.....	....	0	....	.....	...	110	578	0.190	....	....	123 mg. % 9th day
	Febrile	3	103.0	50	0	750	1.033	16	159	832	0.191	1664	0.61	No shock but given L-arterenol
									169*	659	0.257	1318	0.48	3rd to 6th day; highest BUN
L. A.	Oliguric	5	101.8	53	4+	560	1.035	21	19*	121	0.158	256	0.62	92 mg. % on 8th day
	Diuretic	10	99.4	43	4+	4440	1.006	89	41	240	0.172	421	4.01	
	Conval.	29	98.0	42	0	....	1.018	....	120	667	0.180	1150	....	
	Febrile	5	103.8	55	4+	950	1.022	17	140*	421	0.338	948	0.74	No shock but given L-arterenol
	Oliguric†	7	99.2	54	4+	1680	1.030	60	27*	147	0.185	316	1.30	4th to 7th day; highest BUN
P. O.	Diuretic	12	99.2	40	4+	4180	1.010	132	34	185	0.186	308	3.47	133 mg. % on 11th day
	Conval.	36	98.6	37	0	....	1.014	....	105	583	0.180	927	....	

* Indicates that patient was receiving L-arterenol infusion.

† This patient never became oliguric but the study on the seventh day of illness is designated oliguric, since the patient's status at this time was that of early renal failure (note the specific gravity of 1.030). Subsequently, the urine flow increased considerably.

RESULTS

Table 1 summarizes the renal and pertinent clinical and laboratory data. Figure 1 shows graphically the serial inulin and PAH clearances in four patients who did not require pressor drugs; Figure 2 shows two patients who received L-arterenol infusions for hypotension; and in Figure 3 there are two patients who were treated early in the course of their disease with L-arterenol infusion.

Febrile Phase. Six of seven patients studied during the febrile period had normal or slightly increased GFR and ERPF and normal filtration fractions. In these six patients C_{IN} varied between 130 and 160 ml./minute and ERPF between 647 and 900 ml./minute. The filtration fractions ranged between 0.15 and 0.21. The exception, P. O. (Fig. 4), was receiving L-arterenol and exhibited a reduced ERPF, a normal GFR and an increased filtration fraction (a normal response to L-arterenol).[7]

It is of interest that four of the seven patients studied during the febrile period had proteinuria despite a normal GFR at this time. Daily urine volumes varied between 500 to 1,000 cc., and urine specific gravities between 1.015 and 1.033 during the febrile phase. Arterial blood pressures were within the normal range.

Hypotensive Phase. Beginning at about the time of defervescence the hematocrit increases, reflecting loss of plasma. Hypotension and shock may occur in some patients at this time. Shortly after deferverscence moderate to marked decreases in GFR and ERPF occurred in seven patients. One (E. H.) had only minimal changes.

Clinical shock occurred in only two patients (V. R.-C. and S. M.), both of whom developed marked reductions in GFR and ERPF. However, equally severe reductions in clearances occurred in patients F. R. and J. T. (Fig. 1) who had no shock or hypotension, and in P. O. and L. A. (Fig. 3) whose arterial blood pressures were maintained at levels of approximately 120/80 with L-arterenol infusions throughout the defervescent period.

Oliguric Phase. The urine output, which may be low toward the end of the febrile phase, often decreases to oliguric levels during the hypotensive phase. However, some patients go into the oliguric phase without exhibiting hypotension or shock while others, less severely ill, may have no oliguria. The daily urine output fell to 30 ml. in V. R.-C. on the seventh day of illness and to 200 to 300 ml. for one or more days between the fifth and eighth days of illness in three others (F. R., J. T. and L. A.). GFR and ERPF were usually at their minimum values during the oliguric phase.

It is of interest to note that urinary specific gravity was maintained at levels of 1.018 or greater at a time when daily urine volumes and clearances were decreasing rapidly in several patients (J. T., V. R.-C., L. A. and P. O.). Blood urea nitrogen levels usually increased rapidly during this phase.

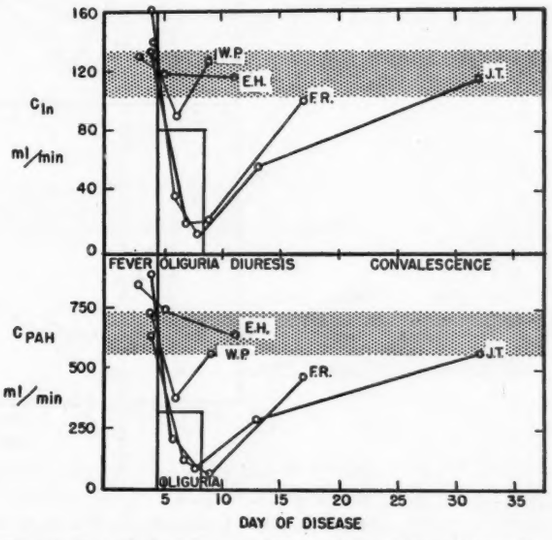

FIG. 1. Renal clearance values in four epidemic hemorrhagic fever patients not exhibiting shock. E. H. and W. P. had mild illness without oliguria. F. R. and J. T. had moderately severe illness with oliguria, the duration of which is shown by the rectangular boxes. The shaded areas depict arbitrary ranges of normal values.

Diuretic Phase. Diuresis developed in the five oliguric patients (F. R., J. T., V. R.-C., L. A. and P. O.) between the ninth and eleventh days of illness. In three others (E. H., W. B. and S. M.) who had no oliguria, diuresis began immediately after defervescence. GFR and ERPF usually began to increase quite early in the diuretic phase. (Figs. 1, 2 and 3.) In patient F. R. (Fig. 1) diuresis occurred with no improvement in a markedly reduced GFR.

Hyposthenuria was the rule during the diuretic phase. Blood urea nitrogen decreased shortly after the onset of diuresis in most patients.

Convalescence. The return of renal function to normal was rapid during convalescence. In seven of our eight patients recovery was complete. ERBF, however, was depressed in several, presumably because of a normchomic anemia.

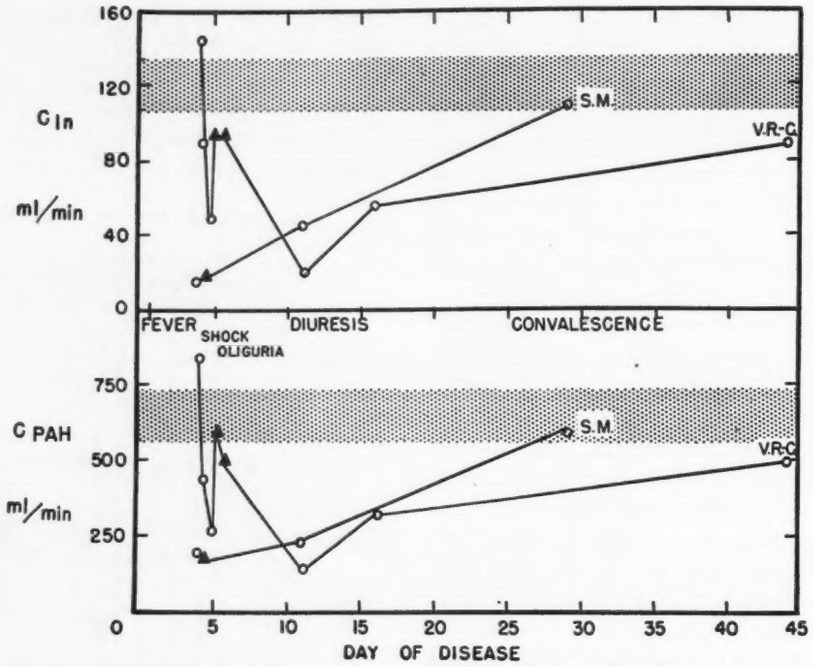

FIG. 2. Renal clearances in two patients in shock treated with L-arterenol during shock phase. Patient V. R.-C. received L-arterenol infusion from the fifth to seventh day of disease, S. M. from the fourth to sixth day of disease. The four points for V. R.-C. on the fifth day (two circles and two triangles) and the first two points from S. M. depict the acute changes effected by L-arterenol. Clearance measurements during L-arterenol infusion are shown by black triangles.

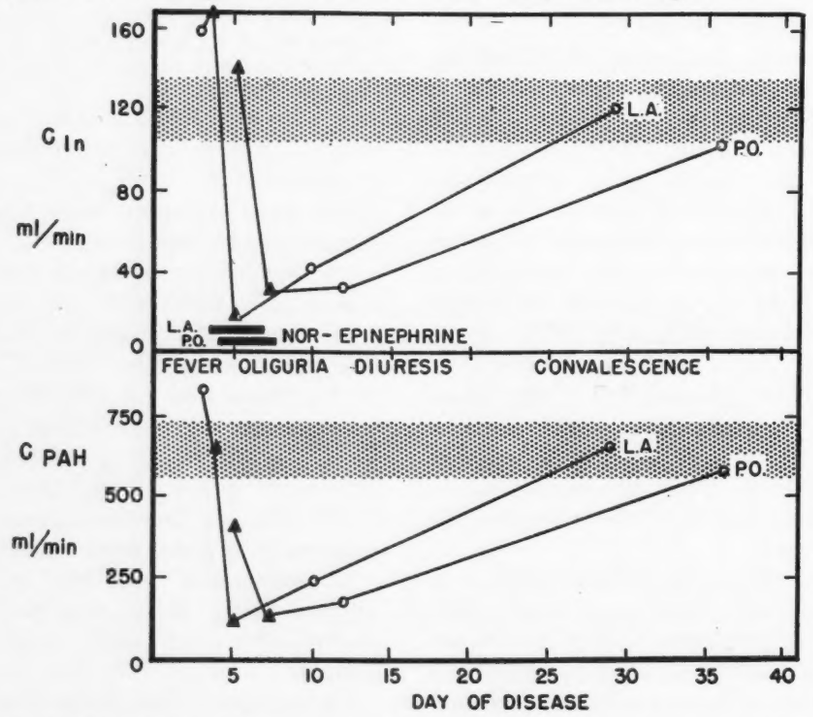

FIG. 3. Renal clearances in two patients given L-arterenol infusions early in epidemic hemorrhagic fever. The first two points for patient L. A. depict the acute changes effected by L-arterenol. Values obtained while L-arterenol was being given are shown by black triangles.

GFR and ERPF had not returned to normal by the forty-fourth day in patient V. R.-C.

Hyposthenuria was the last renal abnormality to disappear. This persisted in five patients (E. H., W. P., J. T., L. A. and P. O.) after clearances had returned to normal.

Effects of L-*Arterenol.* The acute effects of L-arterenol infusion were observed in three patients. L-arterenol was begun during the febrile phase in L. A. (Fig. 3) at a time when renal functions were normal. This decreased the C_{PAH} by 21 per cent and increased the filtration fraction. L-arterenol had relatively little effect on renal hemodynamics in S. M. (Fig. 2) who had developed severe renal damage by the time clearance studies were made on the fourth day. He had been in shock for some hours prior to study for which he was given concentrated human serum albumin. However, he still exhibited an unstable blood pressure and a markedly increased hematocrit.

The effects of L-arterenol on renal functions in the early stages of shock in V. R.-C. are shown in detail in Figure 4. Clearances and filtration fraction on the preceding day had been normal. On the fifth day of illness, while still febrile, he suddenly went into shock. The blood pressure stabilized momentarily at about 100/70 mm. Hg after elevation of the foot of the bed, at which time the clearance study was begun. The blood pressure decreased gradually during the first two clearance periods while GFR and ERPF decreased to levels less than half of normal. L-arterenol raised the blood pressure to about 95/70 mm. Hg and was associated with an increase of C_{IN} and C_{PAH} to almost normal values. When L-arterenol dosage was increased to bring the blood pressure to the range of 130–140/90–100 mm. Hg, GFR and ERPF exhibited considerable variations. The filtration fraction, which had decreased during the period of hypotension, returned to normal as the L-arterenol infusion was continued. Although the patient's arterial pressure was maintained at normotensive levels by controlled L-arterenol infusion throughout the following two days, severe renal damage ensued.

COMMENTS

GFR and ERPF were normal or slightly increased during the febrile phase of hemorrhagic fever even though proteinuria had already developed in most of the patients. Despite considerable fever which might be expected to decrease the filtration fraction,[6] this ratio remained normal. The proteinuria indicates that the glomeruli share in the generalized capillary damage that begins during the latter part of the febrile phase and is one of the dominant features of the hypotensive phase.

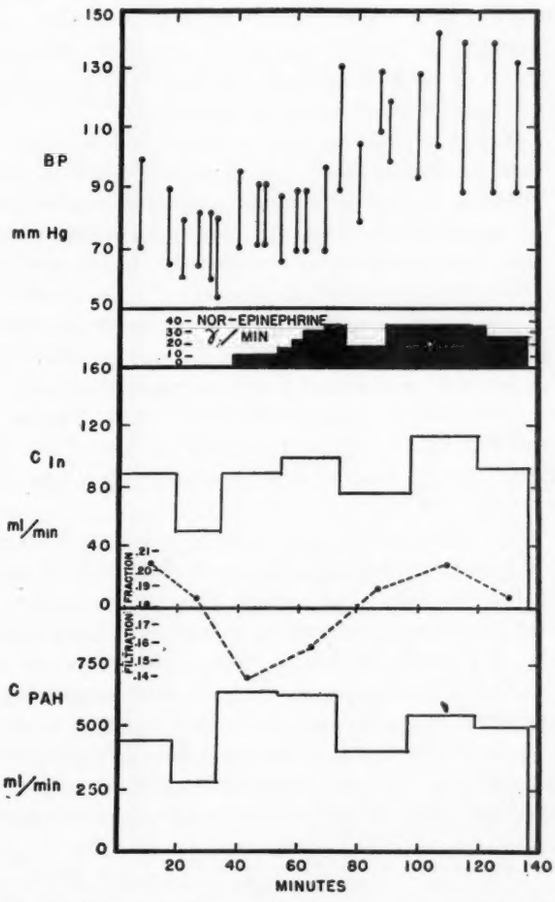

FIG. 4. The acute changes in blood pressure and renal clearances with the beginning of L-arterenol treatment of shock in V. R.-C. See text for description. In this chart each clearance period is shown.

Soon after defervescence, GFR and ERPF* are usually greatly decreased. Although hypotension and shock may occur at this phase of the disease, marked renal function impairment can develop in the absence of these factors. When shock does occur, however, it is reasonable to

* Measurement of renal extraction of PAH was not possible in this study. If extraction is reduced, as seems possible in these patients with severe renal damage, the plasma flow values recorded in this paper are falsely low. Nevertheless, the normal or low filtration fractions observed in these patients suggest that the ERPF values recorded are not greatly different from the true renal plasma flows.

suppose that it adds to the renal damage. Ability to concentrate urine appears to be preserved in many of the patients during the first days of decreased renal clearances. Because of this and because of the marked congestion of the renal medulla,[1,2] renal failure in hemorrhagic fever is probably secondary to alterations in renal vasculature, most likely in the medulla or perhaps the corticomedullary junction. Direct action of the disease agent or some toxin on the renal vasculature could be postulated.

Direct action on the tubules is less likely. Rather, impairment of tubular function, as reflected by decreased concentrating ability at the onset of diuresis, appears to occur several days after renal blood flow has decreased and is probably secondary to anoxia of the tubules. Diuresis may have its onset with no improvement in renal clearances and thus cannot necessarily be taken as a sign that there is no further danger of renal failure. Despite the severe renal damage and functional impairment, the return of renal clearances to normal was rapid in all but one of the patients studied.

Early treatment with L-arterenol was of little value in preventing impairment of renal function in the few patients studied. This confirms other observations.[3] Conversely, it seems unlikely that the reduction in ERPF that L-arterenol may produce (patient L. A., Fig. 3) accentuates the renal damage. Indeed, in V. R.-C. (Fig. 4) who was in early shock, GFR and ERPF increased significantly as L-arterenol brought the blood pressure out of shock levels into the normotensive range.

SUMMARY

1. Serial measurements of C_{IN} and C_{PAH} in eight patients with epidemic hemorrhagic fever have demonstrated the following general pattern: normal or slightly increased clearances in the late febrile stage, falling variably but rapidly over twenty-four to forty-eight hours during the defervescence or "leakage" phase, remaining low during oliguria, and returning to normal over several days or weeks during diuresis and convalescence. Decreased C_{IN} and C_{PAH} occurred in absence of shock or hypotension.

2. The ability to form urine of high specific gravity may persist after the initial decrease in C_{IN} and C_{PAH} but is subsequently lost. The clearances return to normal before the concentrating ability.

3. Early institution of L-arterenol therapy did not prevent marked reduction in renal clearances. This drug, however, did produce an acute but transient increase in clearances as it improved arterial blood pressure in a patient in shock.

Acknowledgment: Sponsored by the Commission on Hemorrhagic Fever of the Armed Forces Epidemiological Board, and supported by the Office of the Surgeon General, Department of the Army.

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Electrolyte Abnormalities in Epidemic Hemorrhagic Fever*

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THE purpose of the present paper is to describe the electrolyte abnormalities observed during the course of hemorrhagic fever, a disease associated with a high incidence of renal failure.[1,2]

MATERIALS AND METHODS

Preliminary observations indicated that patients with mild degrees of hemorrhagic fever exhibited little or no change in serum electrolytes. However, seven patients who appeared moderately ill during the early febrile phase of their disease were selected for daily study of blood and urine electrolytes. Although two of these patients developed shock requiring treatment, and all exhibited considerable renal failure as evidenced by maximum blood urea nitrogen levels that ranged between 123 and 281 mg. per cent with oliguria that varied between 20 and 500 ml. per day, none were considered to have experienced more than a moderately severe illness. None of these patients vomited but during oliguria they were given nothing by mouth, receiving only intravenous infusions of 5 per cent dextrose in water in quantities not in excess of 1 L. per day. With the onset of diuresis the patients were given a regular diet with supplements of citrus fruit juices.

Frequent electrolyte determinations were made in an additional group of nineteen patients who were first studied at the time of development of serious manifestations of hemorrhagic fever. All these patients were critically ill; eight succumbed to their disease.

Sodium and potassium were measured by means of a Baird flame photometer using the lithium internal standard technic. Standard methods were used for the determination of serum chloride, inorganic phosphate, CO_2 combining power, calcium and urea nitrogen. Daily measurements of venous blood pH by the glass electrode were made in two patients. Frequent electrocardiograms were recorded for most patients.

OBSERVATIONS

Daily measurements of serum electrolytes in the seven moderately ill patients revealed few abnormalities until oliguria had been established for several days. At this time a slight to moderate decrease in serum sodium and a slight increase in potassium occurred. (Table 1.) Serum chloride paralleled the sodium values. Serum inorganic phosphate increased to between 3.2 and 6.1 mM/L. Despite the retention of anions during the period of renal failure, blood CO_2 combining power decreased only slightly, minimum values ranging between 20.6 and 24.0 mEq./L. Blood pH, measured daily in two patients, reached minimum values of 7.33 and 7.43 at the time of maximum blood urea nitrogen levels of 278 and 172 mg. per cent, respectively. Serum calcium levels were depressed at the time of increased inorganic phosphate values, ranging between 2.8 and 4.2 mEq./L.

With the onset of diuresis the serum sodium generally increased to normal or slightly above normal values while the potassium usually continued to increase for as long as one week. (Table 1.) At the same time serum inorganic phosphate decreased rapidly and calcium in-

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creased toward normal. Again, the serum chloride paralleled the sodium changes. Peaked T waves were noted in the electrocardiograms taken in patients 1 and 2 (Table I) during the oliguric phase. Curiously, the electrocardiograms reverted to normal in both these patients during the diuretic phase despite further increases in the potassium levels to 6.6 and 6.9 mEq./L. Urinary excretion of sodium, potassium, calcium, chloride and inorganic phosphate was greatly reduced during the hypotensive and oliguric phases but generally increased rapidly during diuresis when the patients were returned to the regular diet.

More marked alterations in serum sodium, potassium and chloride occurred in the nineteen seriously ill patients. All these patients exhibited nausea and vomiting at some time, and in many ingestion of food was reduced or omitted for days. In general, the changes in serum inorganic phosphate, calcium and blood CO_2 combining power were not much different from those that occurred in the seven less seriously ill patients.

Of the twenty-six patients in the two groups nine had serum sodium values of 130 mEq./L. or less during the early diuretic phase. In two this could be attributed in large part to marked excretion with little or no intake of sodium chloride; both these patients improved rapidly when given extra salt. The data for one of these patients are presented in Table II and demonstrate the beneficial effects of adequate salt intake in this circumstance. However, loss of sodium in the urine could not account for the hyponatremia in the other seven patients. The minimum serum sodium levels in these patients during diuresis are given in Table III. The urinary values shown are for the corresponding day and are representative of those observed throughout the preceding days of diuresis. Note that all these patients at the time of hyponatremia were on a regular diet with normal salt complement. The hyponatremia antedated the diuretic phase in three patients. No effort

TABLE I

SERUM SODIUM, POTASSIUM, INORGANIC PHOSPHATE AND CALCIUM DURING OLIGURIA AND DIURESIS IN SEVEN PATIENTS WITH MODERATELY SEVERE HEMORRHAGIC FEVER*

Patient	Days of Oliguria	Sodium		Potassium			Oliguric Phase		Diuretic Phase	
		Min. (Oliguric) (mEq./L.)	Max. (Diuretic) (mEq./L.)	Max. (Oliguric) (mEq./L.)	Max. (Diuretic) (mEq./L.)	Min. (Diuretic) (mEq./L.)	Max. PO_4 (mM/L.)	Ca (mEq./L.)	PO_4 (mM./L.)	Ca (mEq./L.)
1	6	141	161(3)	5.3	6.6(6)	4.1(21)	6.1	2.8	2.5(6)	4.6
2	7	135	140(2)	6.0	6.9(2)	4.6(16)	6.1	3.9	2.7(11)	4.6
3	8	134	146(7)	6.0	5.4(3)	4.2(7)	4.8	4.2	2.3(5)	5.3
4	7	125	148(4)	5.4	6.6(4)	4.2(13)	3.2	4.1	2.4(5)	4.8
5	3	133	146(4)	5.8	6.0(2)	4.6(16)	6.2	3.6	2.3(11)	4.8
6	7	120	146(11)	4.5	6.0(6)	4.0(8)	4.6	4.2	2.4(6)	5.8
7	6	132	141(4)	4.6	5.3(6)	4.6(8)	4.9	3.2	2.4(6)	4.5

* The numbers in parenthesis represent the day of diuresis on which the measurement was made. The inorganic phosphate values recorded for the diuretic phase are the first to be less than 2.8 mM/L. All calcium values were obtained at the same time as the corresponding inorganic phosphate. The values during the oliguric phase were generally made on the last day of oliguria. The patients received nothing by mouth during oliguria but were given a regular diet supplemented with citrus fruit juices at the onset of diuresis.

TABLE II

HYPONATREMIA ASSOCIATED WITH "SALT-LOSING" NEPHROPATHY IN THE DIURETIC PHASE OF HEMORRHAGIC FEVER

Day of Diuresis	Urine Volume (ml./day)	Sodium Intake (mEq./day)	Serum Sodium (mEq./L.)	Urine Sodium	
				mEq./L.	mEq./day
3	1,210	0	128	103	125
4	620	0	125	94	60
5	1,620	0	111	93	150
6	2,460	300	112	97	236
7	3,180	300	129	132	421
8	3,570	0	116	115	419

was made to correct the hyponatremia and all recovered uneventfully.

Serum sodium values in excess of 150 mEq./L. developed during the diuretic phase in six of the twenty-six patients. (Table IV.) The hypernatremia persisted for three to seven days. Three of these patients died, all of causes other than hypernatremia. The hypernatremia followed saline infusion in patients 17 and 19 but patient 18 had received no salt for six days before his maximum sodium value and the remaining three were on the regular diet which probably contributed 100 to 120 mEq. sodium per day. Unfortunately, urinary sodium was measured in only two of the hypernatremic patients. The urinary sodium concentration averaged 22 and 9 mEq./L. and the daily sodium excretion 121 and 36 mEq. in patients 1 and 19, respectively, during the period of hypernatremia.

TABLE III

HYPONATREMIA DURING THE DIURETIC PHASE OF HEMORRHAGIC FEVER PRECEDED BY AND ASSOCIATED WITH DECREASED SODIUM EXCRETION *

Patient	Serum Sodium (mEq./L.)	Day of Diuresis	Urine Volume (ml./day)	Urine Sodium	
				mEq./L.	mEq./day
3	130	2	1,900	14	27
6	127	4	2,040	3	6
10	120	3	2,900	12	35
11	123	7	4,000	5	20
12	129	2	3,000	7	21
13	125	2	4,920	4	20
14	123	3	2,030	13	26
15	124	3	6,330	3	19

* All patients were given a regular diet during the diuretic phase.

Of the twenty-six patients with moderately severe or severe hemorrhagic fever studied, seventeen had potassium levels in excess of 5 mEq./L. during the oliguric or early diuretic phases. Selected data from these patients are shown in Table V which demonstrates a rough correlation between the severity of other manifestations of hemorrhagic fever and the degree of hyperkalemia. The consequences of hyperkalemia were considered by the attending physicians to be severe enough to require therapy in eight of the seventeen patients, three of whom died; hyperkalemia, however, was not considered to be the cause of death in these three patients.

Of the approximately 900 cases of hemorrhagic fever seen by the authors, in only nine instances was hyperkalemia thought to be of critical importance. Hyperkalemia was considered to be the primary cause of death in only two patients, representing less than 5 per cent of the total mortality. Therapy in the nine patients with serious hyperkalemia consisted of intravenous glucose and insulin, calcium gluconate, and cation exchange resin by rectum. Hemodialysis was used in three patients. The two patients who died of hyperkalemia were treated with glucose and insulin only, a therapy known to be of only transient effectiveness.[3] Considering the severity of the renal failure associated with hemorrhagic fever, the inci-

TABLE IV

HYPERNATREMIA DURING THE DIURETIC PHASE OF HEMORRHAGIC FEVER (Serum sodium exceeded 150 mEq./L. for three or more days in each patient.)

Patient	Serum Sodium (mEq./L.)	Day of Diuresis	Urine Volume (ml./day)	Average during Diuresis		Outcome
				Urine (ml./day)	Sodium Intake (mEq./day)	
1	161	3	4,800	4,070	100*	Survived
16	161	5	2,670	2,910	100*	Survived
17	152	6	2,000	1,490	100*	Survived
18	166	8	1,960	2,250	107†	Died
19	171	6	2,260	2,550	0	Died
20	185	8	1,980	3,180	145†	Died

* Estimated sodium content of regular diet.

† Hypernatremia followed saline infusion.

dence of clinically important hyperkalemia is extremely low.

When the electrocardiogram was abnormal during hyperkalemia, it returned to normal rapidly during diuresis, even though the serum potassium may have increased further. (Table I.) Serum sodium and calcium, however, had generally returned to normal at this time.

Potassium deficiency during the diuretic phase was sometimes an important problem in patients who had had considerable vomiting and who had had no food for a number of days. Such patients often were given infusions of 5 per cent dextrose in water with no added potassium. The amount of potassium lost in the urine during the period of diuresis without potassium intake is shown for seven patients in Table VI. Although the potassium content of the vomitus was not measured, the volume of gastric secretion lost was considerable and the negative potassium balances were therefore greater than indicated by the loss in urine. In addition, these patients also lost variable amounts of potassium in the urine during the hypotensive and oliguric phases, which together lasted four to ten days. During these periods the patients received no potassium. (Table VI.) Despite the deficit in body potassium stores, hypokalemia was not marked and three of the seven patients had serum potassium values in the normal range including the patient with the greatest deficit. Although the hypokalemia was not impressive, intravenous administration of potassium chloride produced prompt alleviation of weakness, vomiting and abdominal distention complained of by many of these patients. Also included in Table VI are the data in seven patients who throughout the diuretic phase of their disease received a diet supplemented with citrus fruit juices furnishing approximately 120 mEq. potassium daily. Serum potassium values in these patients remained near or above the upper limits of normal and none complained of the symptoms described in the potassium-deficient patients.

TABLE V

HYPERKALEMIA DURING OLIGURIC PHASE IN RELATION TO SEVERITY OF CERTAIN MANIFESTATIONS OF HEMORRHAGIC FEVER

	Patients with Serum Potassium	
	5–6.8 mEq./L.	>6.8 mEq./L.
Manifestation:		
Total No. of patients	10	8
Febrile phase: Temp. over 102°c. 3–4 days	10	3*
Temp. over 102°c. more than 4 days	0	5
Hypotensive phase: Shock <36 hr	9	3*
Shock >36 hr	1	5
Hemorrhagic manifestations: Petechiae only	9	1
Gross hemorrhages†	1	7
Oliguria: 400 ml. or less for 0–5 days	10	3*
400 ml. or less for more than 5 days	0	5
Maximum BUN: 120–210 mg. %	9	4*
>210 mg. %	1	4
Electrocardiogram: Peaked T wave only	10	3
Additional evidence of hyperkalemia	0	5
Hyperkalemia: No treatment	9	0
Glucose and insulin, resins and/or hemodialysis	1	8

* Unknown in one patient; this patient entered in the less severe category.

† Gross hematuria, hematemesis and/or hemoptysis.

COMMENTS

The hyponatremia, hyperkalemia and retention of anions observed during the oliguric phase of hemorrhagic fever are similar to the changes frequently described in acute renal failure due to a variety of causes. However, considering the severity of the renal failure associated with hemorrhagic fever, the low incidence of ser-

ious hyperkalemia is noteworthy. Likewise, the minimal decrease in blood CO_2 combining power is curious in view of the considerable retention of anions. Hypocalcemia was only rarely associated with evidence of tetany.

During the diuretic phase of hemorrhagic

TABLE VI

POTASSIUM DEFICIENCY DURING DIURETIC PHASE IN PATIENTS WHO VOMITED FREQUENTLY AND RECEIVED NO POTASSIUM

(Data for Patients on Regular Diet during Diuretic Phase Given for Comparative Purposes)

Patient	Day of Diuresis	Previous Total Vomitus (ml.)	Urinary Potassium Loss during Diuresis (mEq.)	Serum Potassium (mEq./L.)
No Potassium Intake (Ave. Daily Potassium Excretion: 72 mEq.)				
11	7	2,410	532	4.5
21	2	4,360	134	3.3
22	3	2,390	365	3.4
23	4	3,940	332	5.0
24	4	1,990	540	3.6
25	4	3,420	261	3.4
26	6	4,300	721	4.7
Regular Diet (Ave. Daily Potassium Excretion: 112 mEq.)				
1	6	0	973	5.6
2	6	0	372	6.1
3	6	0	504	5.4
4	6	0	547	5.0
5	6	0	1632	4.8
6	6	0	345	5.0
7	6	0	345	5.3

fever the following electrolyte alterations were observed: (1) Hyponatremia with or without salt-losing nephropathy; (2) hypernatremia with or without a decrease in urine sodium excretion; (3) hyperkalemia; (4) potassium deficiency with or without hypokalemia.

Hyponatremia following excessive urinary excretion of sodium during the diuresis of early recovery from acute renal failure is well known. However, hyponatremia preceded by and associated with a low sodium excretion was also observed in this study. The serum sodium level is not a reliable guide to the diagnosis of a salt-losing nephropathy and urinary sodium excretion must be followed to evaluate correctly the need for replacement therapy.

Hypernatremia developed in some patients at a time when the urine volume was large and the azotemia was decreasing. Although this appeared to follow saline infusions in several patients, in others it occurred without excessive sodium intake. This phenomenon is similar to that previously described by Luetscher and Blackman[4] in renal failure associated with sulfonamide drug toxicity. They considered this to be the result of damage to a specific portion of the renal tubule.

A continued increase in serum potassium during the first week of diuresis was noted in several patients who had been returned to a regular diet supplemented with citrus fruit juices. This hyperkalemia, however, was but rarely associated with serious symptoms or electrocardiographic abnormality.

Potassium deficiency was common in patients in whom intake of this ion was limited by nausea and vomiting at a time when large amounts were being lost in the urine. Symptoms and signs characteristic of hypokalemia were associated with these circumstances but the serum potassium was often in the normal range and the degree of hypokalemia was never impressive. Nevertheless, intravenous administration of potassium, even when the serum potassium level was high normal, appeared to have prompt and beneficial effects, particularly in several patients who appeared to have paralytic ileus. Observations in dogs[5] have shown that intestinal paralysis can result from a deficiency of intracellular potassium without hypokalemia.

SUMMARY

The following electrolyte abnormalities were observed during the course of hemorrhagic fever: (1) During the oliguric phase, hyponatremia, hyperkalemia, hypocalcemia and retention of anions were common. However, serious hyperkalemia was rarely encountered and acidosis was not severe. (2) During diuresis, hyponatremia occasionally resulted from a "salt-losing" nephropathy but more often was due to unknown causes. The hyperkalemia frequently increased during early diuresis but at this time was not dangerous. Potassium deficiency, associated with the usual symptoms and signs of hypokalemia, sometimes occurred even though hypokalemia was not present.

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L-arterenol in the Treatment of Epidemic Hemorrhagic Fever*

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DIMINISHED vasomotor tone during the febrile phase of hemorrhagic fever is indicated by the development of a flush, dizziness, occasional syncope and postural hypotension.[1] As the shock phase develops with defervescence, the skin frequently remains warm and flushed. Patients dying during this phase of illness exhibit marked capillary dilatation in a number of other areas[2] and effective circulating blood volume is further reduced by loss of plasma from the vascular compartment and by trapping of erythrocytes in dilated small blood vessels.[1,3]

Therapy directed toward correction of the diminished plasma volume by injection of concentrated serum albumin has been of great value but is sometimes inadequate;[4,5] moreover, dangerously large amounts of serum albumin are sometimes required. Because of the demonstrated usefulness of continuous intravenous pressor amine therapy in other types of shock,[6–8] the present study was undertaken to evaluate the effectiveness of L-arterenol in the shock phase of hemorrhagic fever. In addition, it had been suggested[9] that early institution of continuous pressor therapy might control arteriolar dysfunction in such a way as to prevent or modify capillary damage and so protect the patient against the development of renal failure and other serious manifestations characteristic of the disease.[10,11] Accordingly, continuous L-arterenol treatment was instituted prior to the development of the hypotensive phase in a group of patients.

METHOD

L-arterenol in a 5 per cent dextrose in water solution was given by constant intravenous infusion through a polyethylene catheter placed in an ankle, antecubital or femoral vein. The infusion rate was adjusted so as to maintain the systolic blood pressure between 100 and 115 mm. Hg. The dosage of L-arterenol required in patients with shock generally varied between 10 and 320 μg. per minute.

Earlier attempts to maintain the systolic pressure between 120 and 140 mm. Hg were abandoned because of marked fluctuations in pressure at the higher dosage levels required. In addition, the renal plasma flow which was decreased during shock returned toward normal as the blood pressure was raised to 100–115 mm. Hg, but decreased again as the pressure was increased above 120 mm. Hg by larger doses of L-arterenol.[12]

Additional therapy for shock was given in the form of concentrated serum albumin if a rapidly increasing dosage of pressor drug was required to maintain blood pressure, if the hematocrit increased excessively, if the pulse pressure was less than 20 mm. Hg or if the pulse rate consistently exceeded 100. If the serum albumin was not given at such times, increasing amounts of L-arterenol resulted in a further decrease in pulse pressure and occasionally an unobtainable blood pressure.

RESULTS

L-arterenol in the Treatment of Shock in Hemorrhagic Fever. Eleven of the twelve patients in this group (Table 1) were in severe clinical shock when L-arterenol was started. Patient 3 had been in severe shock which had responded partially (pulse rate still increased) to 4 units of serum albumin during the three hours prior to starting L-arterenol. The degree of plasma loss, as reflected by the greatly increased hematocrits shown in Table 1, was considerable in all but one of the patients.

L-arterenol produced an immediate initial decrease in the pulse rate, usually to less than 100, in all patients and an immediate increase in

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blood pressure in the eleven patients who had hypotension prior to drug therapy. An example of the acute effect of L-arterenol on the femoral arterial pressure tracing is shown in Figure 1. Despite a greatly reduced effective circulating blood volume (hematocrit 56), pressor therapy adequate dosage of L-arterenol is demonstrated in Figure 2 which illustrates the course of events in the patient who died in shock. Similar episodes of hypotension or recurrent shock were demonstrated on several occasions in nine of twelve patients when the pressor drug infusion

TABLE I

CONTINUOUS L-ARTERENOL INFUSION IN THE TREATMENT OF SHOCK IN HEMORRHAGIC FEVER

Patient	L-Arterenol			Blood Pressure		Pulse Rate		Maximum Hematocrit	Days from End of Primary Shock to Death
	μg. per Minute	Duration in Hours	Total Mg.	Maximum Control	Initial Response Maximum	Maximum Control	Initial Response Minimum		
1	13 to 24	24	14	98/88	150/128	110	80	60	Survived
2	7 to 30	20	18	82/62	150/102	104	94	66	10
3	10 to 30	56	102	112/85	120/95	138	100	60	2
4	30 to 240	101	189	68/35	164/95	128	78	56	6
5	3 to 10	27	8	90/70	128/96	100	80	58	Survived
6	80 to 320	7½	15	0/0	152/102	?	100	59	Died in primary shock
7	5 to 50	64	88	86/76	120/100	116	106	62	2
8	15 to 27	34	39	90/70	152/102	102	72	61	Survived
9	3 to 13	48	26	70/56	118/88	120	92	49	Survived
10	15 to 80	62	104	80/68	128/98	104	68	66	Survived
11	20 to 40	51	62	90/70	140/100	120	96	58	Survived
12	5 to 10	38	16	86/70	130/94	110	80	60	Survived

not only increased blood pressure within a few minutes but also returned the grossly abnormal pressure curve to normal.

During the course of another study[13] the acute effects of L-arterenol on hemodynamics in the febrile and hypotensive phases of hemorrhagic fever were observed. These data are reproduced in Table II with the author's permission. The three patients in the febrile phase exhibited some hypotension but no clinical evidence of shock. Cardiac index was well above normal in two while peripheral resistance was definitely decreased in all three. L-arterenol increased blood pressure in each instance but increased peripheral resistance only in the patient whose cardiac index fell from an unusually high initial value. L-arterenol increased blood pressure in the two patients in shock. Peripheral resistance, however, was increased slightly in only one.

With the exception of one patient who died in primary shock after seven and one-half hours of treatment, the duration of continuous intravenous pressor drug administration varied between 20 and 101 hours. (Table I.) The dependence of blood pressure on continued was either purposely or inadvertently slowed or stopped.

Shock was diagnosed on clinical evidence and was usually associated with an increasing hematocrit and pulse rate, and decreasing blood and pulse pressures. A narrowed pulse pressure alone could not be relied upon as a good criterion for shock during pressor therapy since the latter in excess doses reduced pulse pressure.

Only three of the twelve patients whose shock was treated with L-arterenol infusion required no supplementary albumin therapy. On the other hand, more than 600 ml. concentrated human serum albumin was required in only three of the twelve patients. Prior to institution of the L-arterenol study, administration of more than 600 ml. albumin was quite common in hemorrhagic fever patients with comparable degrees of clinical shock and hemoconcentration.

After twenty-four to forty-eight hours of pressor drug infusion, the hematocrit generally began to decrease and the dosage of L-arterenol was reduced gradually to avoid the development of hypertension. Pressor therapy was discon-

TABLE II

EFFECT OF L-ARTERENOL ON HEMODYNAMICS IN HEMORRHAGIC FEVER *

Patient †	Phase	Hematocrit	Period	Venous Pressure (mm. Saline)	Mean Arterial Pressure (mm. Hg)	Cardiac Index (L./Min.)	Peripheral Resistance (Units)	T-1824 Circulation Time (Sec.)
17	Febrile	50	Control	65	86	5.0	8.0	10
			L-arterenol	68	115	6.0	9.0	15
29	Febrile	52	Control	70	76	8.0	4.5	25
			L-arterenol	28	112	5.9	10.8	14
16	Febrile	53	Control	25	76	4.6	9.1	12
			L-arterenol	...	83	5.5	8.3	12
8	Hypotensive	51	Control	3	70	3.3	12.0	20
			L-arterenol	12	113	3.5	18.4	16
12A ‡	Hypotensive	54	Control	88	81	3.2	12.0	15
			L-arterenol	108	92	4.1	10.6	10

* The author is indebted to Dr. D. W. Cugell for permission to present these data.

† These patients appear under same numbers in Tables I and III.

‡ This patient does not appear elsewhere in this paper since he received L-arterenol for only one hour.

tinued when 1 to 3 μg. L-arterenol per minute was sufficient to maintain normal blood pressure.

Only one of the twelve patients with severe shock treated with pressor therapy died in the primary shock phase. (Fig. 2.) In retrospect, it was believed that this patient received insufficient plasma volume expander after the second hour of observation. In addition, the L-arterenol infusion accidentally stopped at the ninth hour for fifteen minutes. Subsequently, the patient remained in shock despite heroic therapy and died half an hour later.

Four additional patients treated with L-arterenol died of complications two to ten days after the termination of the primary hypotensive phase. Such deaths were frequently preceded by shock but in these instances the shock was secondary to extreme dehydration, electrolyte disturbances or complicating pulmonary infections.[1] Episodes of this type were treated with continuous intravenous pressor drug, along with other measures to combat the underlying complications in eight critically ill patients in the later phases of hemorrhagic fever. The pressor therapy maintained blood pressure in the normal range in all but one. However, only three survived, the remainder dying in acute pulmonary edema.

Two patients, not included in the present analysis, died in the primary shock phase of hemorrhagic fever despite continuous intravenous pressor drug therapy. These patients were treated before institution of the present

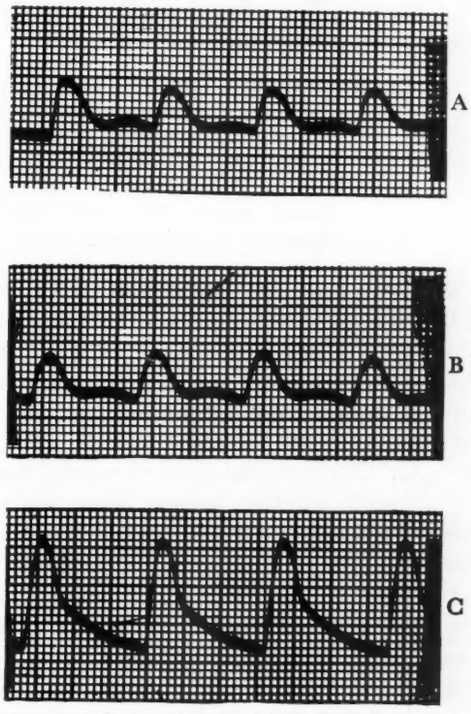

FIG. 1. Effect of L-arterenol on femoral arterial pressure curve during severe shock in hemorrhagic fever (patient 4, Table I). A, pre-treatment blood pressure 68/35, the tracing is grossly abnormal and characteristic of shock. B, one minute after the administration of L-arternol at 30 μg./min., blood pressure 73/45. Within three minutes the blood pressure had reached normal levels. C, tracings after thirty minutes are normal in appearance, blood pressure 150/80.

study. Both received large doses of neosynphrine as well as L-arterenol. The pressor infusion was frequently started and stopped in one of these patients, who at one time remained in shock with unobtainable blood pressure for two and one-half hours before the infusion was restarted.

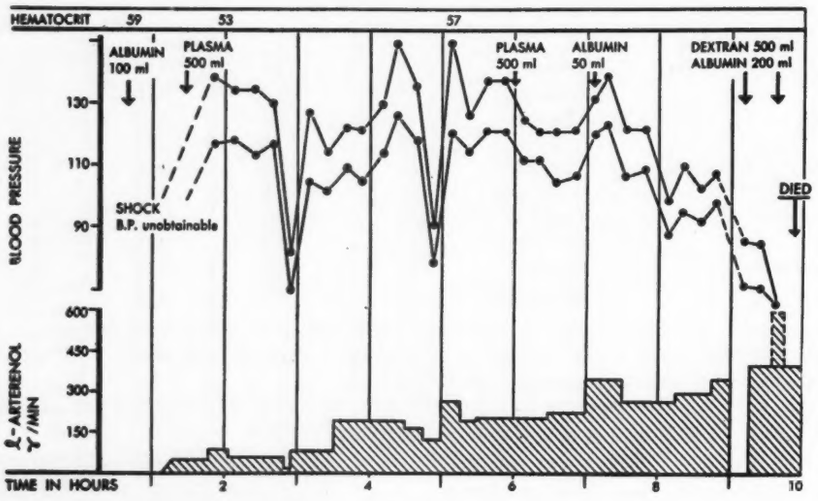

FIG. 2. Example of fatality in severe primary shock in hemorrhagic fever despite continuous L-arterenol infusion (patient 6, Table I and Fig. 3). This patient was admitted in severe shock and blood pressure was unobtainable until given both plasma volume expander and an infusion containing a large amount of L-arterenol. Accidental stopping or slowing of the infusion resulted in marked decrease in blood pressure. The severe shock that followed the second episode did not respond to further plasma volume expanders or heroic pressor therapy.

The other patient likewise remained in shock with unobtainable blood pressure for almost an hour before institution of pressor drug therapy. This patient, in addition, was given no plasma volume expander over a period of seven hours, while the hematocrit increased from fifty-nine to sixty-eight. This occurred just before and during the early part of the pressor drug therapy. Following the episodes described previously increasing doses of L-arterenol and/or neosynephrine to more than 1,000 μg. per minute and liberal amounts of concentrated human serum albumin failed to maintain blood pressure and both patients died in shock.

If the two patients just cited are included in the analysis, three (21 per cent) of fourteen patients whose shock was treated with continuous intravenous pressor therapy drugs died in the primary shock phase, as compared with sixteen (33 per cent) of forty-eight patients whose shock was treated with concentrated serum albumin but not with L-arterenol. These differences are not statistically significant (chi-square test). Approximately one-third of the survivors of primary shock in both groups died during later phases of the disease with a variety of complications.

L-arterenol Treatment Prior to Hypotensive Phase. Eighteen patients were given continuous intravenous pressor therapy prior to the onset of serious hypotension or shock. There was no essential difference in the results in those treated before or after the appearance of proteinuria and the two groups will be considered together. Although prediction of the severity of the subsequent course of hemorrhagic fever during the initial febrile phase cannot be made precisely, there is a reasonable degree of correlation.[11] In any case an effort was made to select patients for the present study who had considerable fever and who appeared quite ill on clinical grounds.

Data concerning the status of these patients at the time of starting L-arterenol infusion, the details of the L-arterenol therapy and data concerned with the evaluation of the severity of the subsequent hypotensive, renal, hemorrhagic and central nervous system manifestations are summarized in Table III. None of the eighteen patients died, six required more than 10 μg. L-arterenol per minute at some time, but only one exhibited any evidence of clinical shock and required a supplementary serum albumin infusion. The course of the latter patient is shown in Figure 3. The incidence of shock requiring

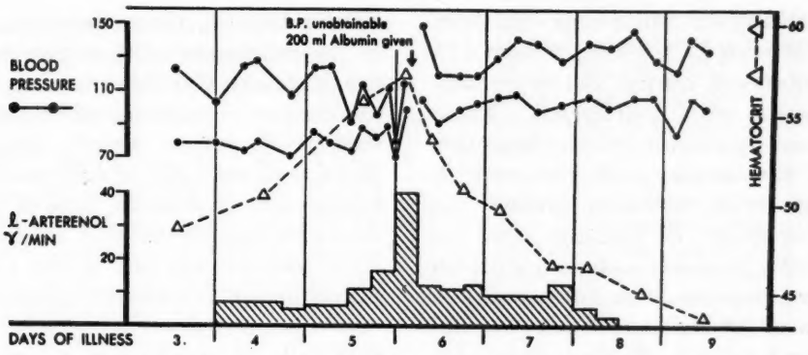

FIG. 3. Example of treatment of hemorrhagic fever by continuous L-arterenol infusion begun before hypotensive phase. Note the gradual increase in hematocrit. During this time the dosage of L-arterenol was gradually increased. At the time of maximum hematocrit, while the patient was receiving very large dosages of L-arterenol, the blood pressure became unobtainable. At this point 200 ml. of serum albumin was given. After this, as the hematocrit gradually decreased, the dosage of L-arterenol could be reduced.

TABLE III

EFFECT OF CONTINUOUS L-ARTERENOL INFUSION STARTED DURING FEBRILE PHASE ON SUBSEQUENT COURSE OF HEMORRHAGIC FEVER

Patient	Status at Start of Therapy			L-Arterenol			Evaluation				Hemorrhagic Manifestations and Mental Status
	Day of Disease	Proteinuria	Hematocrit	Duration in Hours	μg. per Minute		Days Temperature over 102°F.	Lowest Blood Pressure	Maximum Hematocrit	Maximum B.U.N.	
					Start	Maximum					
13	2	0	46	133½	6	28	3	110/70	52	132	Gross hematuria, disoriented
14	2	0	Normal*	74	Low*	Low*	3	Normal*	52	92	None
15	2	0	46	38	4	8	2	110/74	49	36	None
16	2	0	45	105	4	6	2	108/68	52	93	None
17	2	0	48	89	5	10	2	110/74	56	128	None
18	2	0	48	120	5	40	2	98/88	56	184	Hematemesis, hematuria, convulsions, paranoia
19	2	0	45	69	4	8	2	98/68	58	64	None
20	3	0	50	82	4	7	2	106/58	51	17	Gross hematuria
21	3	0	Normal*	60	Low*	Low*	3	Normal*	48	17	None
22	3	0	46	34	6	8	2	120/70	53	18	None
23	3	0	50	64	4	7	2	102/62	53	72	Gross hematuria, paranoia
24	3	0	Normal*	82	Low*	High*	4	Normal*	59	133	Gross hematuria, epistaxis, disoriented
25	3	2+	50	60	21	64	2	86/72	58	27	None
26	3	2+	Normal*	45	Low*	Low*	3	Normal*	48	23	None
27	4	4+	56	24	22	22	2	124/86	56	171	Gross hematuria, restless
28	4	1+	48	68	8	15	3	114/70	58	126	Disoriented, mania
29	5	4+	56	56	5	8	2	102/60	56	49	None
30	5	1+	46	28	3	3	0?	118/64	48	49	None

* Parts of these protocols were lost but summaries were available which described indicated measurements in the terms recorded.

serum albumin therapy in this group was 5 per cent as compared with 21 per cent among 175 other patients observed during the same outbreak not treated with L-arterenol. These differences are not significant by the chi-square test. However, the majority of instances of shock requiring serum albumin among the control group occurred in patients who exhibited appreciable increases in hematocrit. Of forty-four control patients with hematocrits of 55 or greater, thirty (68 per cent) required serum albumin injection for shock. This compares with one of the eight (12 per cent) patients in the early L-arterenol treated group whose hematocrits exceeded 55 and whose shock required albumin administration. This difference is highly significant by the chi-square test.

Despite the probable amelioration of the hypotension and shock by the early institution of L-arterenol therapy in hemorrhagic fever, this procedure did not prevent the development of severe capillary leakage as reflected by greatly increased hematocrits, severe renal failure as evidenced by the maximum blood area nitrogen, or significant hemorrhagic and central nervous system manifestations. (Table III.) The number of treated patients was too small to permit any conclusion as to the effect of early L-arterenol therapy on mortality in hemorrhagic fever.

Complications of Continuous Intravenous L-arterenol. The most common complication of continuous L-arterenol infusions was phlebitis of the vein in which the polyethylene tubing was placed. This was most severe when ankle veins were used for the infusions. No severe phlebitis occurred among eighteen patients in whom the antecubital or femoral veins were utilized. Infiltration of the infusion into the subcutaneous tissues of one patient resulted in severe local vasoconstriction followed by ulceration of the skin. Superficial skin ulcerations occurred in two other patients who had phlebitis only.

COMMENT

That continuous L-arterenol infusion is a useful procedure in the management of severe primary shock in hemorrhagic fever is demonstrated by its initial prompt and beneficial effect on clinical appearance, pulse and blood pressure. Its continued effectiveness throughout the hypotensive phase can be demonstrated by noting the return of hypotension and shock when the infusion is reduced in rate or stopped too soon. Pressor therapy alone, however, rarely suffices in the management of severe shock in hemorrhagic fever. Careful attention must be paid to effective circulating blood volume, and the severely ill patient usually requires additional therapy in the form of concentrated (salt-poor) human serum albumin. Loss of plasma through damaged capillaries may continue for several days and perhaps one of the greatest benefits of continuous L-arterenol infusions is the reduction it permits in the amount of serum albumin that may be required in the treatment of the seriously ill patient.

Three of fourteen patients with severe shock treated with continuous intravenous pressor drugs died in primary shock and the mortality rate in the shock phase for this group was not significantly different from the control group with equally severe shock. However, it is worth noting the mishaps that occurred in the use of L-arterenol infusions in the three patients who died. Unfortunately, the severely ill hemorrhagic fever patient is subject to a wide variety of serious physiologic derangements and complications during the later stages of the disease,[1,3] and tiding a patient over a severe primary shock phase does not assure eventual survival. The evidence at hand suggests that continuous pressor drug infusion represents a valuable adjunct to the management of hemorrhagic fever but the number of patients reported here is small and any conclusion as to the effect of this type of therapy on the over-all mortality rate would be premature.

Institution of continuous intravenous L-arterenol administration during the initial febrile phase of hemorrhagic fever may possibly have a beneficial effect on hypotension, but does not prevent capillary leakage, severe renal failure or serious hemorrhagic or central nervous system manifestations.

SUMMARY

1. Hypotension and shock occurring during the hypotensive phase of hemorrhagic fever responds at least transiently to continuous infusion of L-arterenol.

2. However, decreased circulating plasma volume is an important factor in the etiology of the shock and the judicious use of L-arterenol and concentrated human serum albumin either alone or in combination, as circumstances dictate, appears to be the method of choice for the management of the severely ill patient in this phase of the disease.

3. Early use of continuous intravenous L-arterenol does not prevent the development of severe renal failure and other serious manifestations of hemorrhagic fever.

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Analysis of Sequential Physiologic Derangements in Epidemic Hemorrhagic Fever*

With a Commentary on Management

DAVID P. EARLE, M.D.†

HEMORRHAGIC fever is an acute disease of unknown etiology which is characterized by widespread abnormalities of blood vessels, chiefly arterioles and capillaries. The vascular abnormalities lead to impairment of function in a number of organs. Many of the resulting clinical,[1–8] laboratory,[9–12] functional[13–16] and pathologic[17–20] features have been adequately described. The present paper represents an attempt to correlate these diverse findings in such a way that the clinical course and management of hemorrhagic fever may be considered in terms of the underlying physiologic derangements.

In making this analysis the author has drawn freely upon the ideas and observations of many medical officers who have studied the disease.† Some of the points to be made appear to be well established. Some aspects of the physiologic interpretations are based on data which unfortunately are incomplete, and some of the interpretations are frankly speculative in nature, being supported by the most indirect type of evidence.

† The author is very pleased to express his appreciation of the many ways in which Major John A. Sheedy, Chief of Medicine and Lt. Col. George White, Commanding Officer of the 48th Surgical Hospital (Mobile Army), Col. Richard P. Mason, Col. William E. Stone, Brigadier General L. Holmes Ginn, Major General William E. Shambora and Dr. Joseph E. Smadel made these studies possible and would like to thank them for their many courtesies and excellent suggestions. It will be apparent to the reader of this Symposium that the present paper is possible only because of the efforts and ideas of the author's colleagues at the 48th Hospital during the 1952 fall outbreak and also of the many medical officers who studied the disease during the earlier outbreaks.

The subdivision of the clinical course of hemorrhagic fever into its several phases (febrile, hypotensive, oliguric, diuretic and convalescent) is arbitrary, considerable overlapping of certain features occurring among the several phases, and sometimes in mildly ill patients the hypotensive and oliguric phases may not appear at all. Nevertheless, each of these phases is characterized by a different set of more or less distinct physiologic disturbances, and each appears to follow its predecessor in dependent and logical sequence. This analysis of the underlying physiologic derangements will therefore follow the same sequential pattern rather than consider each function or system individually throughout the entire course of the disease.

INITIAL FEBRILE PHASE

Evidence for small blood vessel dysfunction appears quite early in hemorrhagic fever. A marked, almost characteristic flush of the face, neck and upper thorax together with intense injection of the soft palate and pharynx suggests arteriolar dilatation. This is confirmed by direct microscopic observation of vessels at the base of the finger nail.[21] Likewise, plethysmographic observations,[16] slightly increased renal blood flow[14] and increased cardiac output and decreased peripheral resistance[15] are compatible with arteriolar dilatation at this time. Much of this arteriolar dilatation could be the ordinary response to fever. However, the subsequent appearance of petechiae and of a positive Rumpel-Leedes test[1,5] indicates that capillaries are seriously damaged. Blood platelets begin to decrease in number during the febrile

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phase,[1,7,10] the hematocrit begins to increase with little or no change in total serum proteins[11] and the plasma volume is sometimes slightly reduced.[13] At the same time, proteinuria rather suddenly develops.[1,2,5,7] These observations, taken together, suggest that plasma is beginning to leak out of the vascular system. Many patients complain of considerable thirst at this time. It has been a repeatedly confirmed clinical observation[18,22,23] that administration of fluid to such patients very promptly results in increased abdominal discomfort and lumbar backache, and in some instances produced scleral and conjunctival edema. Apparently, the administered excess fluid simply leaks out into the tissues.

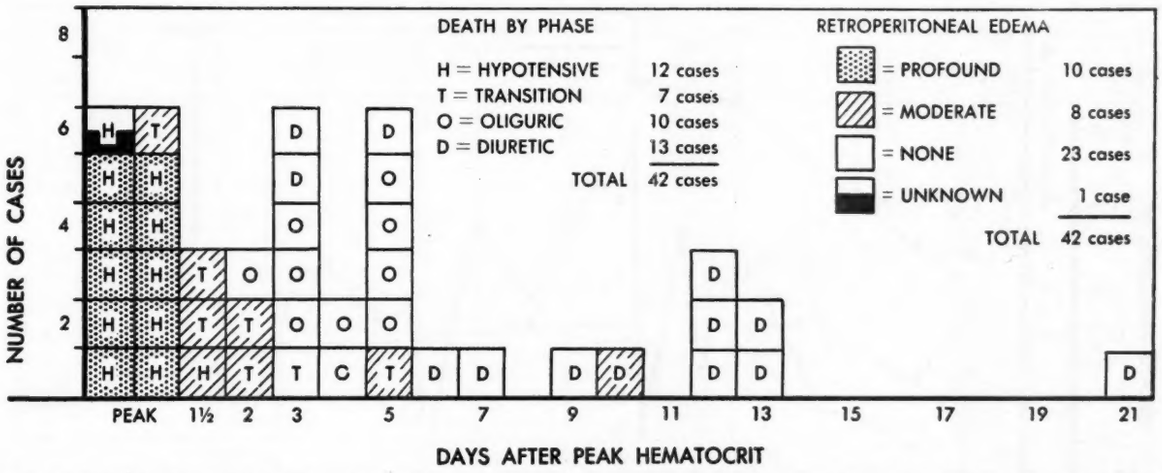


FIG. 1. Death in hemorrhagic fever in relation to phase, time of maximum hematocrit during hypotensive phase and retroperitoneal edema.

Death during the initial phase of epidemic hemorrhagic fever did not occur among the patients who form the basis of this analysis.

HYPOTENSIVE PHASE

Defervescence is often associated with a decreasing blood pressure and sometimes with shock, as evidenced by symptoms and tachycardia. Early primary shock of this type accounted for almost one-third of all deaths in hemorrhagic fever. (Fig. 1.) At least two major factors are concerned in the development of primary shock in this phase: reduced circulating blood volume and loss of arteriolar tone.

Evidence for *loss of plasma through capillary walls* is overwhelming. Patients who died in this phase of the disease were found to have a very large amount of gelatinous retroperitoneal edema,[17–20] with a protein content approximating that of the blood plasma.[24] The presence or absence of retroperitoneal edema was definitely related to the phase of the disease at the time of death, as shown in Figure 1, where the degree of retroperitoneal edema noted in each fatality is distributed in relation to time of maximum hematocrit. This is taken as a clinical guide to the severity of leakage of plasma out of the vascular system, one of the major features of the hypotensive phase. Note that marked retroperitoneal edema was observed in all but one of the patients dying in the primary shock phase, that moderate edema occurred in six of the seven patients dying in the transition phase (i.e., as the hematocrit was falling), while moderate edema was observed in only one of the twenty-three patients dying later in the oliguric and diuretic phases. A sharp increase in the hematocrit not associated with an increase in the serum total protein concentration[11] reflects this loss of plasma from the vascular system. All twelve patients considered to have died in primary shock did so within twenty-four hours of the maximum hematocrit value. (Fig. 1.) Plasma volume, measured either by the T-1824 dye or tagged erythrocyte technic, may be significantly reduced and the rate of dye disappearance considerably increased in the hypotensive phase.[13] Proteinuria is also probably a reflection of the extensive capillary damage. Finally, a persistent increase in finger tip volume following venous occlusion has been demonstrated by a plethysmographic technic during this phase.[16] Some degree of plasma leakage may occur in all but the mildest instances of hemorrhagic fever since the hematocrit may exhibit a

considerable increase even when there is no evidence of shock or hypotension.[8]

A typical example of death during the hypotensive phase is illustrated in Figure 2. Note that both plasma volume replacement (concentrated human serum albumin) and increasing doses of the primary shock in hemorrhagic fever. Clinical observation indicates that the peculiar flushes of the febrile phase persist during shock even after defervescence. The extremities may remain warm despite clinical shock. The pulse pressure usually narrows somewhat during the onset of

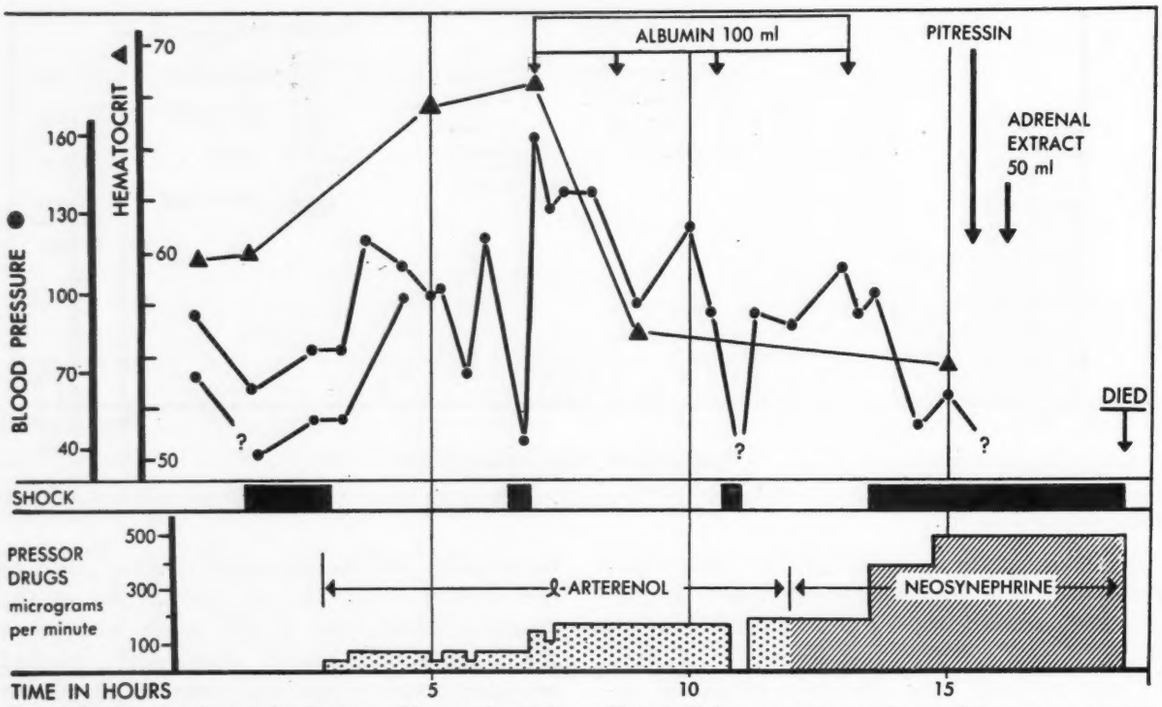


FIG. 2. Death in primary shock phase of hemorrhagic fever. Note initial response to continuous intravenous pressor therapy but increasing requirements during subsequent course, and death after eighteen hours' observation despite 400 ml. concentrated human albumin, pitressin and adrenal cortical extract. Note also shock at eleventh hour when L-arterenol infusion infiltrated into subcutaneous tissue. Blood pressure could be measured only by palpatory method after fifth hour. Marked retroperitoneal edema present at autopsy.

pressor drug given by continuous intravenous infusion failed to maintain this patient's blood pressure.

A *reduction of circulating red blood cell mass* may also begin in the hypotensive phase in severely ill patients.[13] This has occurred in patients with little or no hemorrhage. Hemolysis of significant degree has not yet been demonstrated during this phase of the disease. The reduced circulating red blood cell volume is therefore probably the result of pooling or trapping of erythrocytes in dilated capillaries. This process may occur not only in the renal medulla but also in the gastrointestinal tract, the spleen and in other organs.[17–20]

Evidence of *loss of arteriolar tone* is less direct and clear-cut than that for plasma leakage. Nevertheless, available evidence reviewed subsequently suggests that the vasoconstriction observed in burn shock,[25] a condition characterized by plasma loss, does not occur regularly during shock but in most patients decreased pulse pressure is not marked in relation to the low levels of systolic pressure. Finger tip blood flow is not obviously reduced.[16] Measurements of cardiac output and peripheral resistance during the hypotensive phase unfortunately are meager. Nevertheless, those available indicate that peripheral resistance usually is not increased and may be below normal, while the cardiac output is at or below the lower limits of normal.*[15] Finally, the effect of continuous intravenous L-arterenol during the hypotensive phase of hemorrhagic fever may be cited. Unusually large dosages of this drug may be required to maintain blood pressure in certain patients.[27] In some this may be a reflection of a considerable reduction in circulating blood volume but in others large and increasing amounts of pressor

* Further studies made during the fall 1953 outbreak of hemorrhagic fever have confirmed these observations.[26]

agent are required even though the hematocrit is stable and only slightly increased. (Fig. 3.)

As a result of the small blood vessel dysfunction, and perhaps because of local edema, *blood flow to certain organs is impaired.* This has been demonstrated insofar as the kidneys are concerned,[14] and is suggested by symptoms and the histologic evidence of congested and dilated capillaries in the stomach and sometimes in other organs, including portions of the brain. Although impairment of renal and gastric functions does not contribute to the mortality of the hypotensive phase, it does play an important part in the subsequent stormy course.

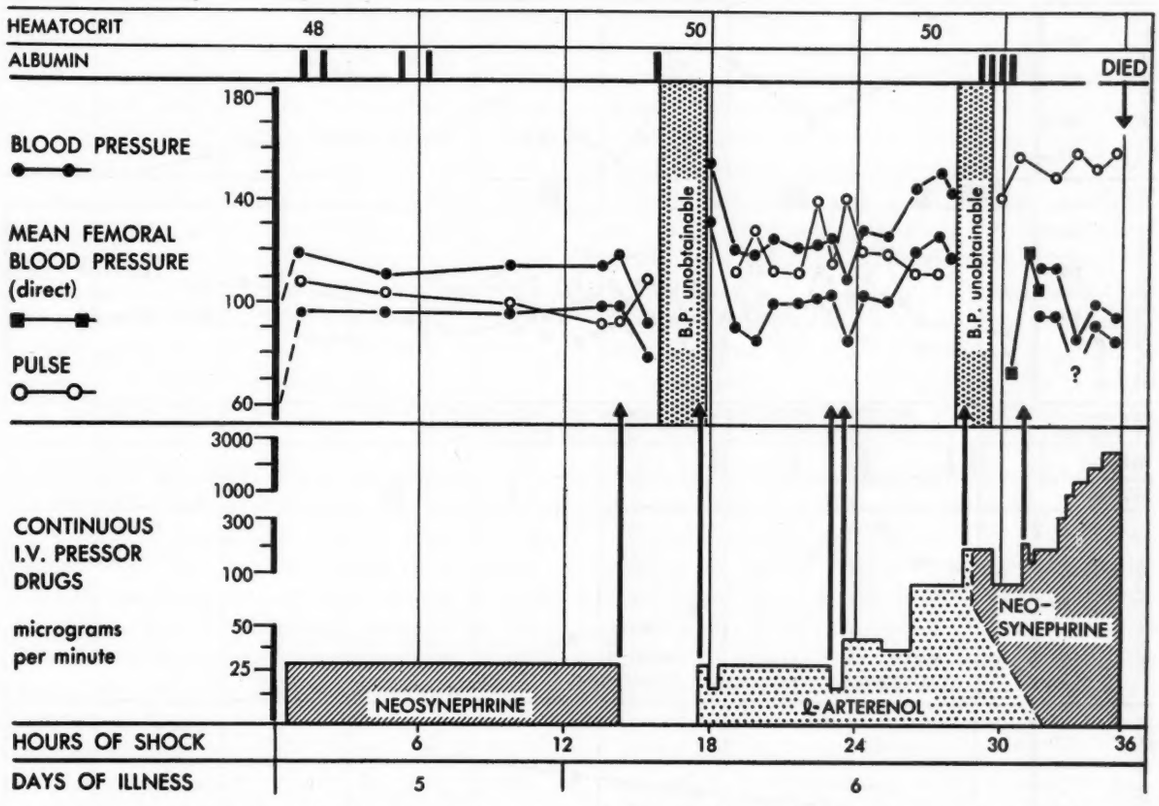


FIG. 3. Example of transition shock in hemorrhagic fever. Note dependency of blood pressure on pressor therapy and relative ineffectiveness of serum albumin therapy despite minimal increase in hematocrit.

Impairment of renal function which usually begins about the time of defervescence may develop independent of shock or even hypotension.[14] This is evidenced by the development of proteinuria, oliguria, impaired renal function and nitrogen retention in patients who have maintained normal blood pressures.[8] Renal failure therefore appears to be related chiefly to decreased renal blood flow which is presumably secondary to the medullary congestion. Except for protein deposits in the glomerular space, some casts in the convoluted tubules and sometimes interstitial edema, the renal cortex usually exhibits no obvious damage at this stage.[17–20]

Hemorrhages, such as ecchymoses at the site of even minor trauma, hematomas, gross hematuria, hematemesis, melena and hemoptysis, begin to appear toward the end of the hypotensive phase when the platelets usually reach their minimum values.[1,5–10] The hemorrhages are rarely large and appear to be chiefly capillary in origin. The gross hematuria can be related to hemorrhages into the pelvis or ureter.[8] Petechial hemorrhages in the central nervous system are not uncommon.[20]

A number of factors appear to be involved in the development of the hemorrhagic phenomena. Capillary damage and platelet reduction are undoubtedly important. Continued stagnation of erythrocytes in widely dilated capillaries persists for days or weeks,[17–20] and such vessels could be assumed to be abnormally fragile. The occurrence and location of hemorrhages are probably conditioned in many instances by

trauma such as venipunctures, hypodermic injections and contusions induced by the patient thrashing about. In addition, other factors may play a secondary role in the development of hemorrhages such as vomiting, coughing, and perhaps also the relative hypervolemia oc-

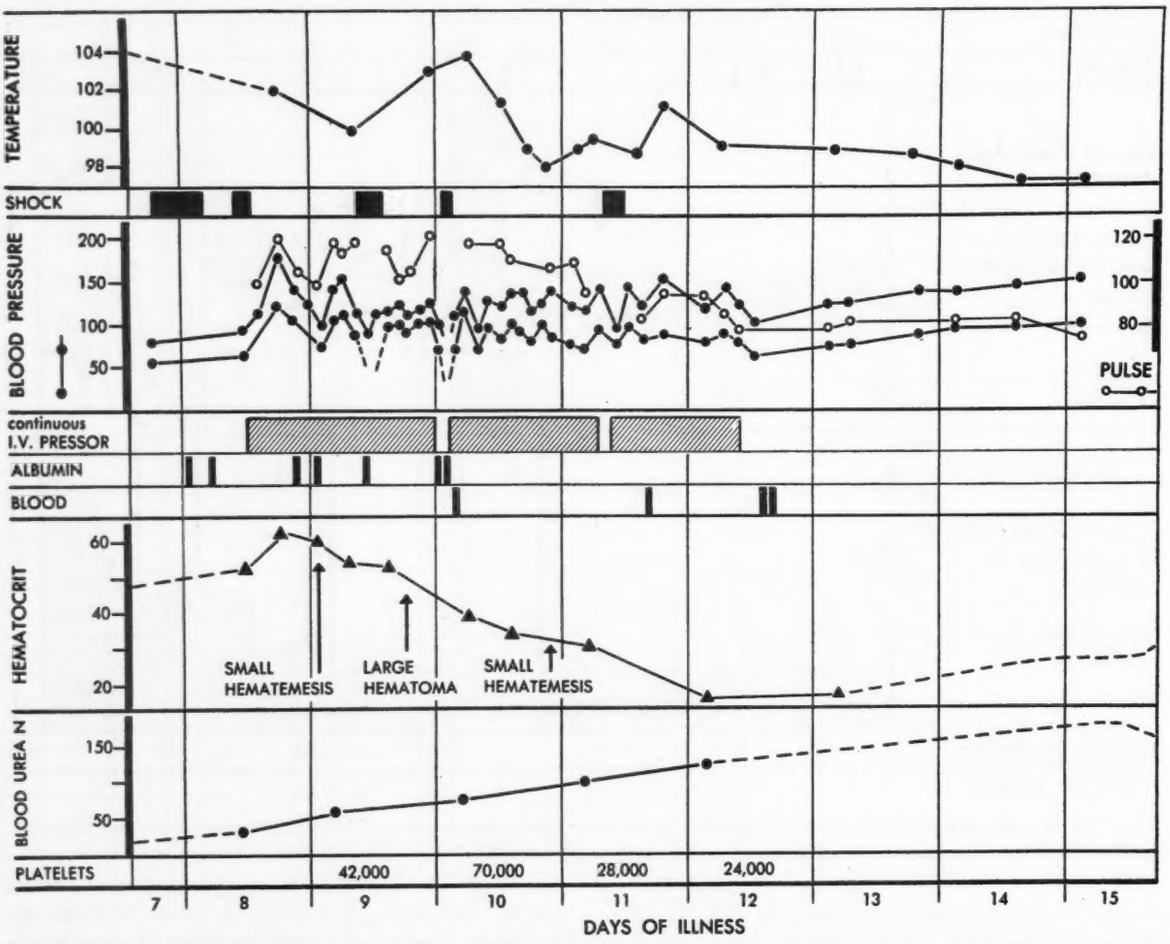


FIG. 4. Example of severe primary shock followed by transitional shock but eventual recovery in hemorrhagic fever. Note decreases in blood pressure and occurrence of shock on tenth and eleventh day when pressor therapy was interrupted for thirty and eighty-five minutes, respectively, even though decrease in hematocrit indicated return of sequestered plasma to effective circulation. External blood loss was small. Anuria and severe oliguria persisted throughout segment of course illustrated.

casionally present at a later stage of the disease (see following text).

Congestion and/or hemorrhages occur in the right auricle, anterior lobe of the pituitary and sometimes in the adrenals.[17–20] Despite this, there is little or no evidence that functional impairment of these organs contributes to the pathogenesis of primary shock in hemorrhagic fever. During the hypotensive phase 17-ketosteroid excretion is reduced,[28] but the marked impairment of renal function at this time renders interpretation of this finding impossible.

OLIGURIC PHASE

Loss of plasma from the vascular system, one of the characteristic features of the hypotensive phase of hemorrhagic fever, appears to be a self-limited process. Generally, the hematocrit begins to decrease after one or two days of maximum elevation, and hypotension and shock usually become less and less of a problem in management. Although oliguria and evidence of renal functional impairment first appear during the early hypotensive phase, the oliguria now becomes more pronounced and urea nitrogen and related substances increase rapidly in the blood. Other symptoms may also appear or become worse, such as mental confusion, nausea, vomiting, dehydration and electrolyte abnormalities. Blood platelets usually begin to increase at this time but they may still be less than 70,000

per mm.[3] and hemorrhagic manifestations may persist.

Transition Period. The decrease in hematocrit may be quite rapid, in some instances falling as much as ten points in twelve hours. Generally, however, the decrease is more gradual, requiring one to three days before stabilizing at or near normal values. Seven of forty-two deaths analyzed[8] occurred during the transition period while the hematocrit was decreasing. All of these patients died in shock, but the pathogenesis of this transition shock appears to be different from that observed during the hypotensive phase.

First, five of these seven patients (all of whom had significant shock during the hypotensive phase) maintained blood pressure at levels of 100/70 mm. Hg or greater, without therapy, for eight to thirty hours during the period of decreasing hematocrit and before the second and fatal bout of shock occurred. Transient hypertensive blood pressures were noted in three of the patients. Second, although retroperitoneal edema was noted in six of the seven autopsies, it was described as mild or moderate in degree, in contrast to the profound edema observed in patients who died in the hypotensive phase. (Fig. 1.) This, together with the observation that total serum protein does not decrease as the hematocrit falls,[11] strongly suggests that at this phase of the disorder plasma is returning from tissue depots to the vascular system. Measurements of plasma volume[13] reveal an increase toward normal at this time, lending further credence to this hypothesis.

It is reasonable, therefore, to attribute the transition shock which occurs as circulating blood volume increases to some type of arteriolar dysfunction. In some instances this may be secondary to such factors as hyperpyrexia, pulmonary infection, central nervous system complication, dehydration or electrolyte abnormalities.[8] Such complicating factors, however, were absent in three of the seven transition period fatalities, and persistent arteriolar dysfunction in such instances perhaps may be the result of the direct action of the etiologic agent or some toxin produced by it. An example of this type is shown in Figure 3. Large continuous doses of intravenous pressor drugs were required to maintain blood pressure in this patient but he eventually expired in shock nevertheless. The hematocrit in this patient never exceeded 50, and presumably loss of plasma from the vascular system was not extensive and played a relatively small role in the pathogenesis of his shock. At autopsy, retroperitoneal edema was present but only in moderate amount.

Another example of transition shock is shown in Figure 4. In this patient, who eventually recovered, continuous intravenous pressor therapy was required to keep the patient out of shock for almost three days after the hematocrit began to decrease. Although some hemorrhage occurred in this patient, the amount of external blood lost was small. Despite this the whole blood volume, measured at a time when the hematocrit had fallen below 40, was only 70 per cent of the expected normal. As indicated previously in connection with the hypotensive phase, it is probable that significant numbers of erythrocytes are trapped in dilated capillaries in a number of organs. Reduction of circulating blood volume on this basis may contribute to the persistence of shock beyond the primary hypotensive phase in rare instances of severe hemorrhagic fever. Beneficial effects of blood transfusions in such circumstances have been demonstrated in a few other patients.

Period of Established Oliguria. Ten of forty-two patients died while oliguric and after the hematocrit had completed its decrease to normal or near normal values.[8] None of these patients had retroperitoneal edema at autopsy (Fig. 1), evidence that the capillary leakage had been repaired by this time.

Dehydration, electrolyte abnormalities and pulmonary complications were important primary or contributory factors to death in this phase.[8] Four of the ten patients died in shock which was secondary to one or more of these factors. An example of shock secondary to pulmonary infection and hyperpyrexia is shown in Figure 5. Although renal failure is at its maximum during this phase,[14] in only one instance was hyperkalemia sufficiently severe to be considered a factor contributing to death. More common was dehydration and potassium deficiency.[8]

Curiously, although most patients in the oliguric phase have marked renal failure and retention of anions such as inorganic phosphate, sulfate and organic acids, blood pH and carbon dioxide CO_2 combining power were almost always within normal limits.[12] The explanation for this is not clear.

Hypertension. Significant hypertension that persisted for more than twenty-four hours was not uncommon during the late oliguric and

early diuretic phases of hemorrhagic fever[1,5,7,8] Blood pressures were sometimes in the range of 160–220/110–120 mm. Hg. Some degree of correlation existed between the incidence of hypertension and the severity of the preceding hypotensive phase, as reflected by the maximum hematocrit, as well as between the incidence of hypertension and the degree of renal failure as reflected by the maximum blood urea nitrogen value.[8] However, many individual exceptions to these correlations existed. Such variations are not surprising in a disease that has such protean manifestations and complications. Present knowledge does not permit assessment of the significance of such possible factors as various pressor substances, hypermetabolism and neurogenic influences in the development of hypertension in hemorrhagic fever. Fluid and electrolyte imbalances, relative hypervolemia[8] and perhaps other consequences undoubtedly modify the pressor response in this phase of the disease.

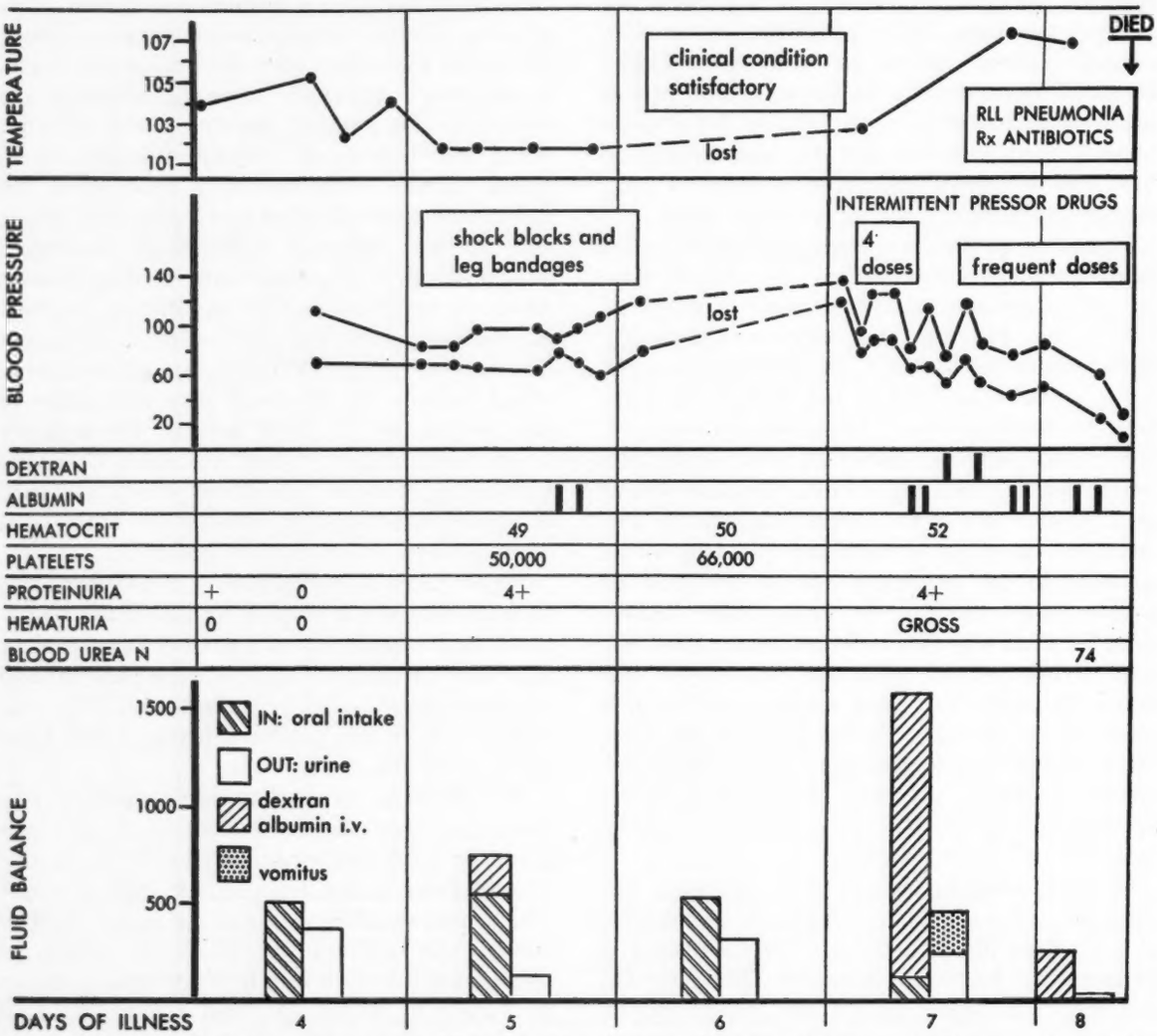


FIG. 5. Example of death in secondary shock during oliguric phase of hemorrhagic fever. Primary shock on fifth day during hypotensive phase was mild. Subsequent slight increase of hematocrit was presumably due to dehydration rather than to continued capillary leakage of plasma. On the seventh day patient developed right lower lobe pneumonia and hyperpyrexia that precipitated shock not responsive to therapy. At autopsy characteristic findings of hemorrhagic fever were present, although there was no retroperitoneal edema. In addition, a patchy pneumonia chiefly in the right lower lobe was noted.

Relative Hypervolemia. During the oliguric phase, usually two to five days after the hematocrit has decreased to normal following its maximum in the hypotensive phase, a syndrome that has many of the characteristics of hypervolemia develops in some patients. Many patients develop for the first time or suffer a marked increase

in symptoms such as nausea and vomiting, mental confusion, restlessness and tremors. At times some patients become maniacal while in others convulsions may develop. On questioning, patients sometimes describe their feelings as "too full in the head," "tense inside," and the like. Such symptoms are frequently associated with the appearance of hypertension. The veins of the hands and forearm may become distended, even when the arm is held straight up in the air. Despite the distended veins venous pressure is not elevated, circulation time (appearance of T-1824) is usually normal, cardiac output is normal or increased, and peripheral resistance usually is in the normal range.[15] The development of an obvious cardiac thrust was observed in a number of these patients and sometimes a gallop rhythm. Peripheral edema is absent, although acute pulmonary edema may develop at this time. Gross hematuria is not uncommonly associated with this syndrome and in a few instances hemoptysis of bright red blood occurred.

TABLE I

"HYPERVOLEMIC" SYNDROME IN HEMORRHAGIC FEVER

Patient	Hypotensive Phase		Status at Onset Syndrome or at Time of Phlebotomy							Clinical*
	Shock	Maximum Hematocrit	Days of Illness	Days After Hematocrit Decrease	HCT.	Blood Urea Nitrogen	Phase	Duration of Hypertension at Time Syndrome Recognized	Blood Pressure	
1	Moderate	54	8	3	45	142	Diuretic	8 hr.	134/110	Distended veins, restless
2	0	53	8	3	38	65	Oliguric	13 hr.	154/110	Confusion, mania
3	0	..	8	4	44	105	Diuretic	3 days	162/100	Restless, convulsion, gross hematuria
4	0	52	8	5	34	111	Diuretic	3½ days	160/100	Distended veins, restless, gross hematuria
5	0	58	8	2	47	126	Diuretic	2½ days	160/110	Distended veins, confused, combative
6	Severe	66	8	2	40	136	Oliguria	1½ days	164/130	Confused, hyperactive, epistaxis
7†	Moderate	61	11	5	41	247	Diuretic	4 days‡	160/110	Distended veins, confused, gross hematuria
8	0	49	10	3	38	94	Diuretic	6 days	165/110	Restless, tremors
12†	Moderate	52	9	3	44	142	Oliguric	3 days	150/110	Distended veins, restless, gross hematuria
			11	5	36	165	Diuretic	5 days	160/120	Distended veins, 2 convulsions, gross hematuria
A-40§	0	56	9	1	46	125	Oliguric	2½ days‡	160/110	Pulmonary edema, restless, gross hematuria
A-41	0	49	6	..	49	...	Oliguric	5 days‡	160/120	Distended veins, pulmonary edema and hemoptysis, convulsion
A-43	Severe	63	10	4	44	188	Oliguric	1 day	160/84	Distended veins, 5 convulsions, gross hematuria
			11	5	38	174	Diuretic	2½ days	196/106	Distended veins, restless
A-45	Moderate	..	8	3	38	146	Oliguric	1 day‡	140/100	Distended veins, restless
A-46	Severe	56	8	2	36	232	Oliguric	2 days‡	144/94	Distended veins, restless, hemoptysis

* Only marked symptoms are listed.
† These patients appear in Table III under same numbers.
‡ Hypertension and/or symptoms developed or were exaggerated during infusions of hypertonic solutions.
§ Patients designated "A" died and are listed under same numbers in Table VIII of reference 8.

This syndrome was thought to be a major or

TABLE II

EFFECT OF PHLEBOTOMY ON "HYPERVOLEMIC" SYNDROME

*Effect of Phlebotomy**

Patient†	Days of Illness	Blood Pressure		Duration	Hematuria‡		Symptomatic Response§
		Before	After		Before	After	
1	8	134/78	68/40	10 min.	Microscopic	0	None
2	8	154/110	128/80	Permanent	0	0	Excellent
3	8	162/100	128/84	Permanent (except for 2 hr. increase)	Gross	0	Excellent
4	8	160/100	140/90	3½ hr.	Gross	1/H.P.F.	Good
5	8	160/110	142/78	5½ hr.	Microscopic	0	Good
6	8	164/130	144/96	10 min.	Microscopic	Microscopic	None
7	11	160/110	110/75	1 day (3 later transient increases)	Gross	0	Good
8	10	165/110	128/78	1½ hr.	Microscopic	0	Fair
12	9	150/110	138/110	.....	Gross	0 (24 hr.)	None
	11	160/120	154/118	.....	Gross	4/H.P.F.	Fair
A-43	10	160/84	138/90	2 hr.	Gross	0	Good (transient)
	11	196/106	150/90	2 hr.	0	0	None (died 5 days later)
A-45	8	140/100	124/90	9 hr.	50/H.P.F.	2/H.P.F.	None (died 9 hr. later)

Summary of Effects of Phlebotomy
(*Thirteen Observations*)

	Response				Total
	None	Fair	Good	Excellent	
Hypertension	2	7	1	2	12
Hematuria	1	0	4	6	11
Symptoms	5	2	4	2	13

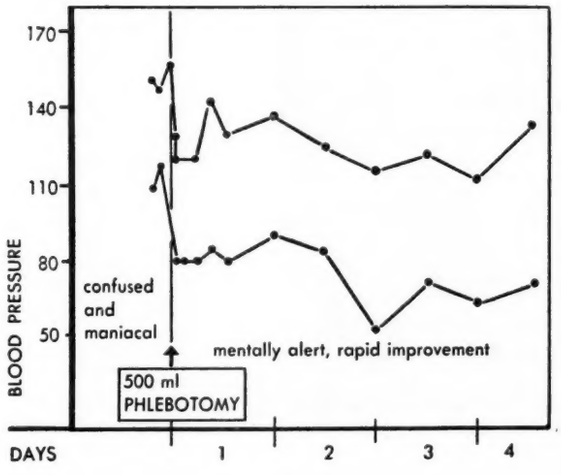
* 500–600 ml. in all patients except for 300 ml. in A-45.

† See Table I for details of clinical status at time of phlebotomy.

‡ H.P.F. = high power field.

§ Excellent: immediate, rapid and permanent improvement of all symptoms; good: immediate, steady improvement in two or more major symptoms; fair: definite but slower or only transient improvement.

significant contributory cause of death in six of the forty-two fatalities analyzed.[8] Death in these instances could usually be directly attributed to the consequences of pulmonary hemorrhage and/or edema or to convulsions. The chief clinical features in fourteen patients thought to



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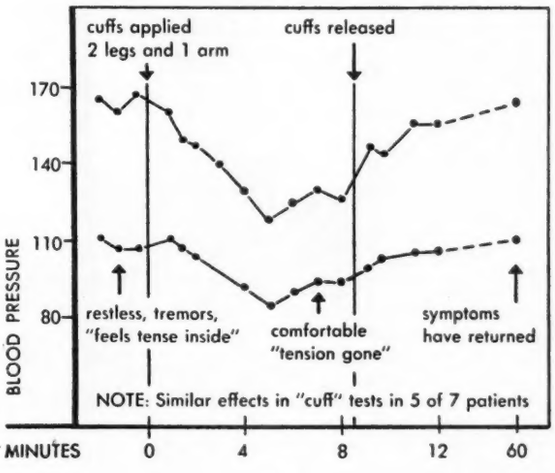

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FIG. 6. Effect of 500 ml. phlebotomy on symptoms and blood pressure—hypervolemic syndrome in hemorrhagic fever.

FIG. 7. Effect of "bloodless" phlebotomy on symptoms and blood pressure—hypervolemic syndrome in hemorrhagic fever.

have had the hypervolemic syndrome are listed in Table I. In several instances the syndrome appeared to be precipitated or at least aggravated by the intravenous administration of fluid.

One or more of the symptoms and signs described may occur in patients who have no evidence of hypervolemia. Some observers of hemorrhagic fever have suggested that the hyperdynamic circulatory features could be the result of hypermetabolism, as in hyperthyroidism. However, no abnormalities have ever been noted in the thyroid at autopsy and there is no clinical evidence other than rapid peripheral blood flow to suggest hyperthyroidism in this phase of hemorrhagic fever. Indeed, bradycardia rather than tachycardia is a common feature of the "hypervolemic" syndrome. Further, many of these symptoms and signs are noted in patients with renal failure or "uremia" due to conditions not ordinarily associated with hypervolemia. Impairment of blood flow in several vital organs probably could explain some of the individual symptoms and signs. Nevertheless, it is difficult to ignore the hypothesis that the full-blown syndrome, especially when the veins are distended and evidence for congestive heart failure is lacking, is at least in part a result of hypervolemia. The occurrence of the syndrome shortly after sequestered plasma has returned to the vascular system, its precipitation by the administration of excessive intravenous fluids (especially when hypertonic), the characteristic mental and motor agitation in contrast to the usual lethargy and coma common in other "uremias," and the beneficial effects of phlebotomy all strengthen the suspicion that hypervolemia merits serious consideration as a basic factor in this phase of the disease.

The effects of phlebotomy in thirteen episodes thought to represent hypervolemia are summarized in Table II. The effects may be immediate, quite dramatic and sometimes permanent. Prior attempts to reduce blood pressure and relieve symptoms by spinal fluid drainage (spinal fluid pressure was sometimes increased), intravenous magnesium sulfate, digitalization and sedation were unsuccessful in several of these patients.

An example of the effect of a 500 ml. phlebotomy on the blood pressure is shown in Figure 6, while the effect of a "bloodless phlebotomy," achieved by inflation cuffs around three extremities, is shown in Figure 7. The latter experiments, which were transiently effective in five of seven instances, suggest that phlebotomy exerted its action through a volume effect rather than by removal of some pressor substance. Phlebotomy

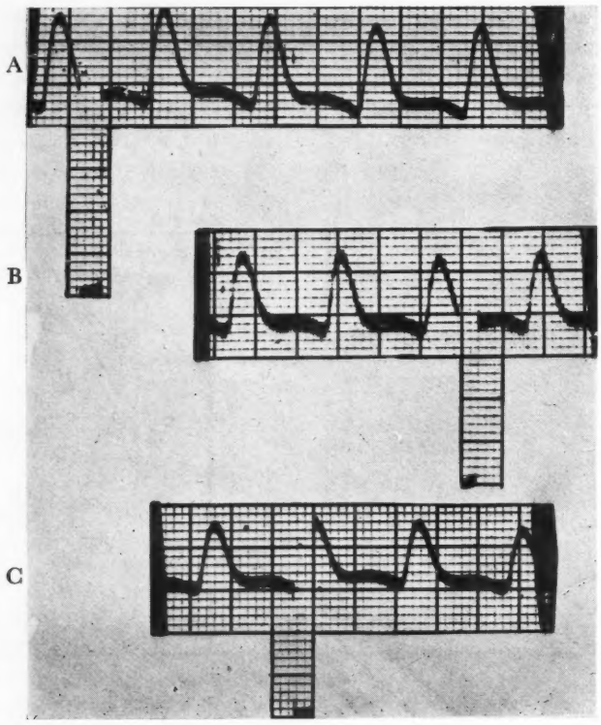


FIG. 8. Effect of 500 ml. phlebotomy on femoral arterial pressure tracing—hypervolemic syndrome in hemorrhagic fever. A, control, blood pressure 160/110 mm. Hg; B, during phlebotomy, blood pressure 130/90 mm. Hg; C, ten minutes after phlebotomy, blood pressure 110/75 mm. Hg. Note persistence of abnormal form of pressure curve (rapid decrease pressure during diastole, absent dicrotic notch) despite marked decrease in both systolic and diastolic pressures.

of the magnitude used in these studies has little or no effect on blood pressure in normal subjects or in patients with essential hypertension.

Phlebotomy reduced to normal the cardiac output in two of three patients with the hypervolemic syndrome and hypotension. (Table III.) A phlebotomy in the third patient, who had had a previous phlebotomy one and one-half days earlier, produced no change in a normal cardiac output.

The effect of a phlebotomy on the femoral arterial pressure tracing (patient 7 of Table III) is shown in Figure 8. Note the abnormal form of the pressure curve, i.e., rapid fall of pressure during diastole with no dicrotic notch. This rapid "run-off" persisted after the pressure fell to

TABLE III

EFFECT OF PHLEBOTOMY ON HEMODYNAMICS DURING "HYPERVOLEMIC" SYNDROME IN HEMORRHAGIC FEVER

Patient	Period	Venous Pressure (mm. H_2O)	Mean Arterial Pressure (mm. Hg)	Cardiac Index (L./min.)	Peripheral Resistance (Units)	T-1824 Circulation Time (Secs.)
7	Control	60	120	6.8	7.0	10
	Phlebotomy	78	99	3.7	14.0	10
12	Control	40	124	3.0	24.0	12
	Phlebotomy	28	118	2.9	24.7	10
13	Control	..	110	3.8	28.9	..
	Phlebotomy	..	90	2.8	32.1	..

a normal value following phlebotomy. Such tracings suggest that the blood is circulating in a relatively rigid vascular system.

Although the plasma which was lost through damaged capillaries during the hypotensive phase has now returned to the vascular system, regions. Reduction of renal blood flow at these times has been demonstrated even in the absence of shock or hypotension,[14] while clinical symptoms suggest that blood flow in organs such as the stomach and perhaps the brain is also decreased.

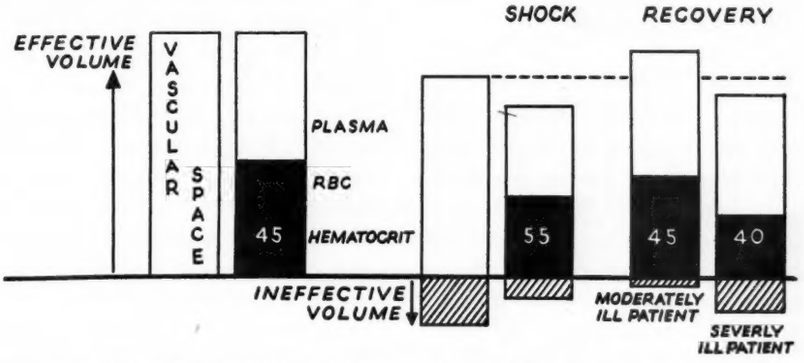


FIG. 9. Relation between blood volume and available vascular space, a possible explanation for "relative hypervolemia" in hemorrhagic fever.

circulating blood volume is not greater than normal and, indeed, may be low normal or even less than normal.[13] A moderate reduction in circulating red blood cell mass is quite common at this stage of the disease among patients who have suffered a severe hypotensive phase.[13]

How, then, is it possible for the hypervolemic syndrome to occur at a time when circulating blood volume is normal or reduced? This question caused considerable concern during the first few phlebotomies. Nevertheless, it appears possible to develop an hypothesis that could account for a "relative hypervolemia" in hemorrhagic fever, even though effective circulating blood volume is decreased. Such an explanation is illustrated in Figure 9 and requires three circumstances: loss of plasma from and then return to the vascular system; persistent pooling or trapping of erythrocytes away from effective circulation; and a reduction of "available vascular space" that persists after the return of sequestered plasma to the vascular system. The first two circumstances have been discussed in preceding sections and appear to be supported by adequate evidence. That available vascular space is reduced during the hypotensive, oliguric and early diuretic phases of hemorrhagic fever is suggested by several considerations. Dilated and congested small blood vessels persist throughout these phases of the disease in the renal medulla, stomach and other areas.[17–20] The histologic appearance of the small blood vessels suggests that little blood could flow in these

An increase in hematocrit to 55 per cent is not uncommon during the hypotensive phase of hemorrhagic fever. It can be calculated that such an increase in a patient whose normal blood volume is 5.5 L. but who has lost or trapped off from the circulation 500 ml. erythrocytes, indicates a 40 per cent reduction in circulating blood volume. The rapid loss of this volume in a patient whose arterioles are dilated night be expected to produce shock. However, patients with hemorrhagic fever may have hematocrits as high as 55 or even 60 per cent with no evidence of shock.[8] This too might be explained on the basis of a concomitant reduction in available vascular space.

The last column in Figure 9 illustrates a possible explanation for continued ("transition") shock which has been observed in a few very severely ill patients even after the sequestered plasma has returned to the vascular system and even though the available vascular space might still be reduced. This requires either the loss or trapping of large numbers of red blood cells, a phenomenon that has probably occurred in a few patients. (Fig. 4.)

The relation of pulmonary edema to the hypervolemic syndrome is not clear although the two are frequently associated. It is difficult to explain a direct relationship unless a considerable portion of the pulmonary vascular bed is not available to the circulating blood volume, thus diverting excess blood to uninvolved areas of the lungs. This situation probably existed in

some of the patients with extensive pulmonary infection or intra-alveolar hemorrhages. However, other circumstances exist in the severely ill hemorrhagic fever patient which have been advanced as causes of pulmonary edema in other conditions. These include central nervous system lesions[29] and potassium deficiency especially when extra sodium is administered.[30]

DIURETIC PHASE

Diuresis may begin abruptly, usually after three to five days of oliguria, but sometimes may develop in patients who have had a relatively mild illness without oliguria.[1,4,7,14] The diuresis is not a reflection of mobilization of the edema fluid of the earlier hypotensive phase since it usually begins several days after resorption of the edema fluid. As shown in Figure 1, retroperitoneal edema was noted in only one of the thirteen patients who died in the diuretic phase. Further, diuresis is frequently initiated at a time when patients are moderately or severely dehydrated. Presumably, residual damage to the renal tubules accounts for the diuresis, although the mechanism for its initiation is not clear. In any event, diuresis has been observed to take place while the renal blood flow and glomerular filtration rate were greatly reduced.[14] The specific gravity of the urine is 1.010 or less during early diuresis. Pitressin and fluid restriction have little or no effect on the diuresis.

As diuresis develops the majority of patients begin to improve rapidly, eat more and regain weight. Blood urea nitrogen usually continues to increase during the first few days of diuresis but then rapidly returns to normal as renal function improves, although renal concentrating ability may remain impaired for many weeks, occasionally for months. However, the onset of a considerable diuresis in patients who are already severely dehydrated and whose caloric intake has been greatly limited for seven to ten days can contribute to further serious fluid and electrolyte imbalances. Thirteen of the forty-two deaths analyzed[8] occurred in the diuretic phase. Nine of these patients died in late shock, which in most instances could be attributed in whole or in part to dehydration and electrolyte abnormalities. Such late, or secondary, shock again precipitates oliguria or anuria, and if sufficiently prolonged or repeated will lead to renewed renal failure and a reversal of the downward trend of the blood urea nitrogen. Other complications, particularly pulmonary infections, were common in the diuretic phase and frequently contributed to death.

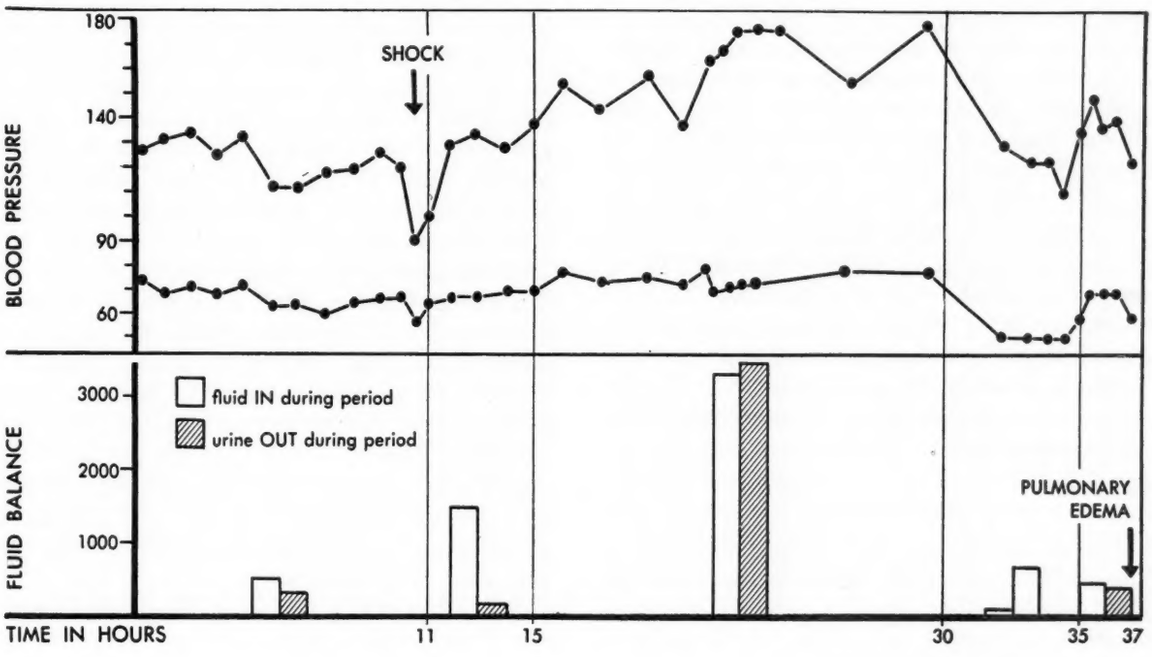
Maintenance of proper fluid balance may be extremely difficult during the diuretic phase. Urinary output is frequently in the range of 3 to 6 L. daily and occasionally reaches 8 L. daily. If output is allowed to exceed intake for even short periods of time, loss of fluid from the vascular space may be sufficient to produce shock. Conversely, if intake exceeds output, hypertension, pulmonary edema and the hypervolemic syndrome may be precipitated with fatal results. An example of these phenomena in a patient with hemorrhagic fever is given in Figure 10. The net balance of fluid over a few hours that represented the difference between shock and pulmonary edema has been observed in a few other patients to be as small as 200 to 500 ml. A secondary rise in hematocrit, associated with an increase in total serum protein, reflects serious dehydration. In such instances diurnal variations in hematocrit and total serum protein values can be observed. The patients are able to drink enough fluids during the day to keep pace with or exceed the urinary output, and by evening may have a normal hematocrit. At night, however, the diuresis persists while fluid intake is usually reduced. As a result the early morning hematocrit may exceed the evening value by five to ten points. The difficulty in regulating fluid balance, together with several other factors which developed in earlier phases of the disease but which persist into the diuretic period, collectively suggest the term "limited homeostasis." The factors involved are as follows: (1) Effective circulating blood volume may occasionally still be reduced[13] by virtue of continued trapping of erythrocytes or prior hemorrhages, along with dehydration. (2) Available vascular space may still be reduced since histologic preparations indicate that dilated and congested small blood vessels are still present in patients who died in the diuretic phase.[17–20] Blood flow to the kidneys is still reduced,[14] as it probably is in other organs as well. (3) Patients who have had a moderately severe or severe course are considerably dehydrated by the end of the oliguric phase. Some have lost as much as 20 pounds by this time. The extracellular fluid space, therefore, is probably greatly reduced. (4) The severely ill patient continues to have nausea and vomiting despite the onset of diuresis. Not only does this contribute to further fluid and electrolyte abnormalities but requires that all fluids and

calories be given intravenously. Too rapid administration of fluid will soon tax the capacity of the reduced vascular space and may produce or exaggerate hypertension, the hypervolemic syndrome and perhaps pulmonary edema.

Thus despite a subnormal circulating blood volume the reduced available vascular space limits the positive fluid balance that may be achieved over any given period of time by intravenous fluids. On the other hand, a negative fluid balance will soon result in a further decrease in blood volume, hypotension and shock, since the interstitial fluid volume is so greatly reduced that ineffective amounts of water can be shifted into the vascular system to meet the emergency. It is therefore essential that the considerable diuresis be matched by intravenous fluids.

This serious fluid volume problem is frequently complicated by a wide variety of electrolyte abnormalities.[12] Hyperkalemia may continue to be a problem in the early diuretic phase, or at any time when further episodes of shock precipitate oliguria and renewed renal failure. However, a deficit in total body potassium is much more common in the late diuretic phase, especially in patients who have had considerable vomiting.[12] Such potassium deficiency is sometimes associated with hypokalemia and symptoms.

Hyponatremia and a considerable deficit in total body stores of sodium may occur in patients who excrete large amounts of salt in the diuretic urine of the late recovery phase. However, hypernatremia can be produced easily by overenthusiastic administration of saline solu-



SUMMARY OF FLUID BALANCE FOR 37 HOURS

IN:	TOTAL FLUID	+ 5660 ml
OUT:	Urine	− 4930 ml
	Vomitus	− 570 ml
	TOTAL	− 5500 ml
GROSS BALANCE		+ 160 ml
INSENSIBLE LOSS		− 750 ml
NET BALANCE		− 590 ml

FIG. 10. Example of limited homeostasis during diuretic phase of hemorrhagic fever. Observations made on fourteenth and fifteenth day of illness. Death occurred on sixteenth day, twenty hours after study. Patient was very dehydrated at start of observations having been in negative fluid balance for many days. Note response of shock and blood pressure to increased fluids between eleventh and fifteenth hours. Also note decrease in blood pressure between thirtieth and thirty-fifth hours when output was allowed to exceed intake. Pulmonary edema occurred in last period when intravenous fluids were increased even though net balance was just barely positive during this time. (Note: Right-hand column, bottom line in 30–35 hour box should be cross-hatched.)

tions, although this phenomenon has also been noted in patients who have had no salt intake for days.[12]

CONVALESCENCE

Although convalescence may be prolonged, permanent organic or functional residua have been very rare even among the most severely ill patients.[7,8,31] Permanent neurologic defects have been reported in patients who have presumably suffered hemorrhages into the central nervous system during the early phases of the disease. Despite the impressive pathologic changes in the right auricle, anterior pituitary and adrenals, no evidence of impaired function of these organs has been observed among recovered patients. Kidney function, at least as measured by simple clinical tests, is also normal at the end of the convalescent period in all but a handful of patients who still were unable to concentrate urine normally more than 100 days after onset of illness.

MANAGEMENT

Several antibiotics and sulfonamides have been tried in the early stages of hemorrhagic fever without any obvious beneficial effects. Convalescent serum and whole blood likewise have been disappointing, although these agents probably have not yet had a fair trial since administration was usually begun in the hypotensive phase after vascular damage was already evident Recent studies[32] suggest that cortisone, begun within seventy-two hours of onset of symptoms, may have an ameliorating effect on fever and general symptoms, and perhaps on the degree of proteinuria and nitrogen retention. However, some cortisone patients died and many others exhibited all the usual manifestations of hemorrhagic fever. At present, therefore, the treatment of hemorrhagic fever is supportive in nature. The abnormalities that develop in the course of hemorrhagic fever are so varied and extensive that the management of each patient requires a careful evaluation of all clinical and laboratory manifestations in terms of the underlying disturbances in physiology.

Many of the technics of management to be outlined here have been described in other reports.[22,23,27] The present consideration makes no effort to give complete details for the management of hemorrhagic fever. Rather, it is an attempt to present the rationale, based on available knowledge of the disease, for the technics used in the treatment of patients at the Hemorrhagic Fever Center during the fall of 1952.

Early hospitalization, before the periods of expected hypotension and hemorrhagic phenomena, is important. This requires that patients be evacuated to the hospital as soon as the diagnosis is suspected for the disease can rarely be definitely diagnosed before the third or fourth day of illness. Transportation to the hospital should be as rapid and non-traumatic as possible. From the onset of illness patients should be protected from physical trauma of even the mildest sort. During the recent outbreak in Korea, helicopters afforded rapid and non-traumatic evacuation.

Good nursing care is an essential part of the treatment. Since medical management is based on the course of signs, symptoms and laboratory findings, frequent observation of the patient by nurses and attendants, as well as by medical personnel, is recommended. Special emphasis should be placed on the need for frequent, accurate and prompt recording of fluid intake and output (including urine and vomitus), temperature, pulse rate, blood pressure and all new signs or symptoms.

Sedation. Mild sedation with barbiturates and occasionally with meperidine hydrochloride for pain, discomfort or restlessness may be required in some patients during the febrile phase. During the hypotensive phase continued but cautious sedation may be required, especially when nausea and vomiting are prominent features. Meperidine hydrochloride is usually satisfactory. Repeated intravenous doses of 10 mg. may be more effective than larger doses by other routes, and moreover make overdosage less likely when shock is present. Increased requirements for sedation are characteristic of the late oliguric and early diuretic phases of hemorrhagic fever, especially when hypertension is present. Apprehension, mental confusion and agitation rapidly increase in severity, at times requiring restraint. Convulsions may occur at this time. Retching and vomiting may become almost constant. Since all these factors increase the hemorrhagic phenomena, adequate sedation is essential.

Diet. In general, a low salt, high carbohydrate diet is recommended until diuresis is well established and convalescence definite. During the early phases of the disease a liquid diet is tolerated better than others, and lends itself most readily to accurate fluid intake

records. Potassium-containing foods including citrus fruit juices should be avoided during the oliguric phase. However, nausea and vomiting often preclude any oral intake and necessitate intravenous carbohydrate administration. Progressive change from liquid to soft diets is indicated during convalescence as gastrointestinal function improves. Frequent small feedings may be required at first in patients who have been severely ill.

Fluid Balance. It appears wise to maintain the patient in as normal water balance as is possible throughout the course of the illness; but if any error is made, it should be in the direction of dehydration. Despite a febrile course of several days, and even extreme thirst, the temptation to allow the patient to drink large quantities of fluid must be strenuously resisted. Overhydration during the febrile and hypotensive phases leads to increase of symptoms such as backache, abdominal distress, nausea and the like.[9,18,19,22,23] In addition, overhydration increases the amount of edema in the bulbar, retroperitoneal and other areas involved in the capillary leakage characteristic of the hypotensive phase. Finally, excess fluid administered at this time increases the load put on the cardiovascular system in the oliguric phase when the plasma lost through damaged capillaries returns to the vascular system.

The most practical approach appears to be that of giving the patient as much fluid as he loses in the urine and vomitus, assuming insensible loss to be 700 ml. daily, and probably giving at least 1,000 ml. fluid daily. If overhydration is present on admission, less fluid should be administered. If intravenous fluid is required, it should be given very slowly in the form of 5 per cent dextrose in water. Evidence is accumulating that administration of the required fluid containing larger amounts of dextrose may be given by constant intravenous infusion through a polyethylene catheter placed in a large vein. But rapid administration of hypertonic fluids is to be strictly avoided, especially in the oliguric and early diuretic phases.

Once diuresis is established, great attention must be paid to water balance. Since in many patients interstitial fluid and effective blood volumes are low at this time, and since diuresis may amount to 3 to 8 L. daily, hypotension and shock can easily be produced if intake is inadequate. Nausea, vomiting or poor gastrointestinal absorption may still be present so that intravenous fluids are frequently required. The fluid may be isotonic (5 per cent dextrose in water) if the total serum protein level is normal, or hypotonic if the protein level is high. However, an excess of fluids given intravenously produces hypertension, pulmonary edema and the hypervolemic syndrome. In patients who have been severely ill with hemorrhagic fever, the difference between dehydration and shock as opposed to hypervolemia and edema may be only 200 ml. Careful and critical quantitative control of water balance is therefore essential in all but the mildest cases in the diuretic phase. Fluid regulation is greatly simplified if an indwelling catheter is placed in the bladder. Frequent checks on intake and output are required, sometimes at half-hour intervals in the severely ill patient.

Even patients with a daily water exchange of only 3 to 4 L. may show marked swings in hematocrit depending on the water balance of the preceding six to ten hours. Discharge from observation, therefore, is unwise until adequate renal concentrating ability has returned.

If hypodermoclyses are used in the diuretic phase, the fluids must be hypotonic, for 5 per cent dextrose in water is hypertonic to interstitial fluid and will withdraw fluid from the patient's own limited stores.

Electrolyte Abnormalities. Potassium: Hyperkalemia of some degree is common during the late oliguric and early diuretic phase[12] but usually requires no therapy. In some instances, however it may become a serious problem. When present to a serious degree, hyperkalemia is difficult to treat. Large amounts of glucose intravenously are contraindicated in early recovery, and the effect of insulin is transient. Nevertheless, 5 per cent dextrose in water and insulin by intravenous drip is useful. Cation exchange resins can be given by rectum to remove potassium but in the dehydrated patient great care must be taken to remove the resin after a few hours to avoid an inspissated mass that can cause bowel obstruction. The artificial kidney is only rarely indicated, and even then should be used with great caution in view of the wide variety of abnormalities present in the severely ill hemorrhagic fever patient. During the diuretic phase the potassium balance soon becomes negative since oral intake of food generally has been nil and since potassium is being lost in the vomitus and also in urine as soon as diuresis is established. Moderate hypokalemia

may develop but symptoms of potassium deficit such as weakness and atonia of the intestinal tract may arise when the plasma potassium is normal or even slightly increased.[12] The latter situation occurs occasionally in very dehydrated patients whose serum protein level is increased. The symptoms of hypokalemia respond readily to administration of potassium.

Sodium: Hyponatremia is common during the hypotensive and oliguric phases, and at times may be extreme.[12] However, much of the hyponatremia appears to be the result of internal redistribution and will not respond readily to salt administration. In other instances, however, large amounts of sodium may be lost in the urine once diuresis is well established. Physiologic saline infusions are indicated in this circumstance but must be given with caution for excess saline can easily produce a marked and serious hypernatremia in these patients.

Hypotension and Shock. Hypotension does not develop in every patient with hemorrhagic fever and when present frequently requires no antishock measures. However, blood pressure and pulse rate should be measured at least every two hours toward the end of the febrile phase. When the systolic blood pressure is decreasing and approaches 100 mm. Hg and the pulse increases to more than 100 beats per minute, measurements should be made more frequently and the patient observed closely for other signs of shock. The hematocrit should be measured two or three times daily toward the end of the febrile phase and throughout the hypotensive phase in the severely ill patient.

Shock may develop even though the extremities remain warm and dry. Mild shock often responds to simple measures such as the Trendelenburg position and elastic bandages applied to the lower extremities. However, shock is sometimes severe enough to require prompt and active treatment and has been one of the frequent causes of death in hemorrhagic fever.

When reduction in plasma volume is excessive, as indicated by severe hypotension, clinical shock and a hematocrit greater than 55, concentrated human salt-poor albumin appears to be the logical therapy. Its effect, however, may be transient when capillary leakage is severe. Usually one to two units are given at one time and followed by subsequent similar doses as indicated. Care should be taken not to administer serum albumin after the hematocrit has definitely begun to decrease, indicating that the sequestered plasma is now returning to the vascular system. When more than six units of albumin have been required to treat shock, eventual recovery has been rare. Excessive administration during the hypotensive phase leads to a greater load on the vascular system after the capillary leakage has been repaired and the plasma has been reabsorbed. Blood transfusions are contraindicated during the hypotensive phase when the hematocrit is increased.

When shock is evident in the hypotensive phase of hemorrhagic fever without a considerable increase in the hematocrit, early use of a continuous intravenous drip of L-arterenol is indicated. The details of the use of L-arterenol in hemorrhagic fever have been presented elsewhere.[27]

Occasionally in severely ill patients shock persists after a decrease in hematocrit indicates return of sequestered plasma to the vascular system. Sometimes this is due to continued arteriolar dysfunction which can be treated with L-arterenol. On other occasions shock during this transition period may be the result, at least in part, of decreased circulating red blood cell volume produced by trapping of erthyrocytes in dilated capillaries, by hemorrhage or by both. This circumstance is suggested by a continued decrease in hematocrit to well below normal values in obviously dehydrated patients. Blood transfusions are indicated under these conditions.

Shock may also occur later in the oliguric and diuretic phases and may be secondary to severe pulmonary infection or to dehydration often associated with electrolyte abnormalities (vide supra). Continuous L-arterenol infusion may again be helpful but therapy directed toward correction of the precipitating factors is the logical approach.

"Relative" Hypervolemia. Phlebotomy may be indicated during the late oliguric phase if evidence for the syndrome of "relative" hypervolemia develops. Established hypertension, distended veins, rapid circulation, increased cardiac thrust, gallop rhythm, pulmonary hemorrhage or edema, increased restlessness, mental confusion and convulsions are all factors to be considered carefully in arriving at a decision to perform phlebotomy. Phlebotomy is not always effective, or may sometimes produce only a transient effect. However, it may at times result in striking benefits. Some indication of

the effectiveness of phlebotomy in any given instance may be gained from a "bloodless" phlebotomy. Blood pressure cuffs are placed around both thighs and one arm and then inflated to a pressure approximately 10 mm. Hg below the diastolic pressure measured in the other arm. Careful note is made of changes in symptomatology and blood pressure. If phlebotomy is decided upon, it should be performed slowly. Should more than one 500 ml. phlebotomy be required the blood may be saved in order that the cells, washed with saline, can be returned to the patient several days later. The hypervolemic syndrome may be present when diuresis begins; under such circumstances merely allowing urinary output to exceed fluid intake sometimes effects adequate control.

Considerable clinical judgment is required during this period. Patients who run a severe course with nausea and vomiting need continuous intravenous infusions to combat dehydration and maintain some carbohydrate intake. Thus as soon as hypervolemia is not a serious problem cautious administration of fluid under close supervision is indicated. Five per cent dextrose in water is preferable for this purpose in most instances. Hypertonic fluids and saline should be strictly avoided at this time because of their penchant for producing or aggravating hypertension and hypervolemia, unless it can be demonstrated that large amounts of salt are being lost in the urine.

DISCUSSION AND SUMMARY

Hemorrhagic fever may be divided into several phases each with its own characteristic features: the febrile, hypotensive, oliguric, diuretic and convalescent. Deaths occur with approximately equal frequency in the hypotensive, oliguric and diuretic phases.

So many physiologic processes can be disturbed to such variable degrees in hemorrhagic fever, and such a wide variety of complications may arise, that it is difficult to find two patients whose clinical courses are exactly alike. The management of each patient therefore requires careful evaluation and interpretation of each of his manifestations of hemorrhagic fever.

Widespread abnormalities of small blood vessels appear to be the chief characteristics of the early phases of hemorrhagic fever and set the stage for subsequent developments. Physiologic and clinical observations suggest that arteriolar dilatation occurs during the febrile and hypotensive phase. There is also incontrovertible evidence that protein-rich plasma is lost through damaged capillaries and that erythrocytes are pooled and trapped in dilated capillaries. These processes not only can produce shock if they are extensive enough but they also impair circulation in certain organs and areas, even in the absence of hypotension or shock. Hemorrhagic manifestations are capillary in origin and are associated with thrombocytopenia. Plasma loss and arteriolar dysfunction, however, are self-limited in duration and, for unknown reasons, the sequestered plasma rather abruptly returns to the vascular system and active circulation. Despite this, the subsequent course of hemorrhagic fever may be quite stormy, for several features that developed in the hypotensive phase may persist into the later stages. Capillaries in affected organs remain dilated and congested with erythrocytes, which probably prolongs the impaired blood flow and functions of these organs.

In the oliguric phase, impaired renal function, oliguria and electrolyte abnormalities dominate; in addition, in certain patients hypertension develops and some exhibit a hypervolemic syndrome. The latter may occur even though the circulating blood volume may be less than normal and should therefore be termed "relative hypervolemia." Continued trapping of erythrocytes in dilated capillaries, along with dehydration not only is responsible for the reduced circulating blood volume but also for a reduction in blood flow to various organs and for a contraction of available vascular space, which together furnish the basis for the development of relative hypervolemia.

Although diuresis heralds the beginning of convalescence in the majority of patients, a daily urinary output of 3 to 8 L. in patients who have had a stormy course and are already dehydrated contributes to further serious fluid and electrolyte imbalances. If the fluid output exceeds intake for very long, shock soon develops since the grossly contracted interstitial fluid space is unable to buffer the drain of fluid volume from the vascular system. Conversely, if fluid intake exceeds output, hypertension, pulmonary edema and the hypervolemic syndrome may result. The patients in this stage appear to be in a state that might be termed "limited homeostasis."

Convalescence may be prolonged but recovery is generally complete in the survivors.

In the absence of specific therapy, management of the varied and serious clinical manifestations of hemorrhagic fever must be based on an understanding of the physiologic disturbances. When loss of plasma from the vascular system and arteriolar dysfunction produce shock which does not respond to simple measures, concentrated human serum albumin and continuous intravenous administration of pressor drugs are the most effective therapy. Excessive administration of fluid must be avoided during the febrile and hypotensive phases since the added fluid simply leaks out of the damaged capillaries and thus increases edema and symptoms. Adequate sedation and avoidance of trauma, retching and coughing may minimize the hemorrhagic manifestations which are common in the febrile and hypotensive phases. The most important problems of the oliguric and diuretic phases are concerned with fluid and electrolyte abnormalities of various sorts. Careful laboratory studies are required for their proper management. Phlebotomy is indicated for the hypervolemic syndrome, especially when associated with convulsions or marked mental agitation. Careful adjustment of fluid intake to urinary output is important during the early diuretic period.

The outline of physiologic disturbances here presented is not intended to be a complete consideration of all aspects of the disease. For instance, gross and microscopic examination of the anterior pituitary and adrenal glands from fatal cases reveals considerable damage.[17–20] Although eosinophil counts and ketosteroid excretions[28] suggest that functional impairment can occur, these findings are difficult to interpret. Further, the fact that certain aspects of the gross disturbances in physiology have been stressed does not imply that other more subtle or as yet undetermined factors are not equally important. A variety of nervous, humoral and metabolic abnormalities undoubtedly contributes to, or play important roles in, the pathogenesis of the clinical manifestations of hemorrhagic fever.

Although many of the clinical manifestations of hemorrhagic fever may be explained in sequential physiologic terms, the factors responsible for the vascular abnormalities which directly or indirectly produce these manifestations are not known. There are many unanswered problems. Does the etiologic agent or some toxin produced by it attack both arterioles and capillaries, or are changes in the capillaries secondary to arteriolar dysfunction? Why the peculiar distribution of vascular abnormalities (renal medulla, anterior pituitary, adrenals, right auricle, lymph nodes, stomach, certain areas of the skin, retroperitoneal space)? What causes the thrombocytopenia? What is the reason for the rather rapid return of plasma to the vascular system that marks the end of the hypotensive phase? What role, if any, in the clinical course is played by the extensive lesion of the arterior pituitary gland? What are the factors responsible for the hypertension frequently noted in the late oliguric or early diuretic phase?

The over-all course of hemorrhagic fever and the evidence of widespread involvement of small blood vessels are quite suggestive of a rickettsial disease. In many respects hemorrhagic fever is similar to Rocky Mountain spotted fever although the progression of the manifestations is much more rapid and complex in hemorrhagic fever. Similarities to scrub typhus and leptospirosis are also apparent. Many of the individual manifestations of hemorrhagic fever similarly have their counterparts in other diseases. Thus the problem of plasma loss is not entirely unrelated to that seen in burns or peritonitis. The hemorrhagic manifestations are quite similar to those of the thrombocytopenic purpuras and radiation sickness. Although apparently unique in pathologic findings the clinical features of the renal aspects of hemorrhagic fever are those of any other acute renal failure. The hypervolemic syndrome observed in hemorrhagic fever has many features which have been described in normal subjects given repeated doses of serum albumin,[33] and in patients with renal failure given excessive fluid,[34–36] acute glomerulonephritis[37] and perhaps in several other situations. The occurrence of apparent hypervolemia in the presence of a reduced or low normal blood volume requires the concept of "relative hypervolemia." The "limited homeostasis" of the diuretic phase is not unlike that seen in infants suffering from diseases that produce fluid and electrolyte deficiencies. Taken as a whole, however, hemorrhagic fever appears to be unique in its startling morphologic organ damage, in its wide variety of physiologic and biochemical abnormalities and in its rapid development of a confusing array of clinical manifestations.

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End of Symposium on Epidemic Hemorrhagic Fever

Seminars on Liver Disease

Viral Hepatitis*

Problems and Progress to 1954

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SEVERAL comprehensive reviews of viral hepatitis have been published during recent years.[5a,6a,7b] Few major advances have resulted since the publication of these reviews in spite of continued intensive studies of various aspects of the disease. The main obstacle to further progress continues to be the failure to find an animal host, other than man, which consistently shows signs, symptoms, lesions or specific serologic reactions pathogenic of infection with the hepatitis viruses. Various workers have provided evidence of propagation in the fertile hen-egg[1,2] but proof of this has been obtained only by testing of the egg material in man and other investigators have been unable to confirm these results. Likewise, favorable results with a skin test, employing ultraviolet irradiated infected egg amniotic fluid as an antigen, have been obtained.[3] However, consistent production of satisfactory lots of antigen has not been possible, there is no method for standardization or assay of antigen except by human tests and others have been unable to confirm the observed results to date. Another skin test antigen[4] prepared from infected mouse spleen has been reported to give encouraging results but likewise has not been confirmed. Finally, all efforts to develop specific serologic tests have met with failure. Thus most of the advances concerning the etiologic agents has been the result of investigations carried out in human volunteers during the past fifteen years supplemented by extensive epidemiologic and clinical studies before and during the same period. During the past few years some of the concepts regarding viral hepatitis have been further confirmed, extended or revised. The objective of the present report is to consider these aspects rather than to review the subject of viral hepatitis as a whole.

ETIOLOGY

The term "viral hepatitis" will be used for reference to those forms of hepatitis that are caused by two or more hepatotropic, filterable, infectious agents, not yet identifiable by specific serologic or cultural methods, which produce a systemic disease in which a characteristic type of liver injury is the outstanding result of human infection. As such, the syndrome of "viral hepatitis" includes infectious or infective hepatitis, "catarrhal" jaundice, epidemic hepatitis or jaundice, homologous serum hepatitis or jaundice, post-transfusion hepatitis, post-vaccinal hepatitis and post-inoculation or syringe hepatitis.

The etiologic agents responsible for the syndromes of hepatitis under consideration have many properties that justify their tentative classification as viruses.[5a,b,c,6a,7a,b] A variety of observations indicate that hepatitis viruses possess a high degree of resistance to many agents or conditions that inhibit or destroy most other infectious agents.

Epidemiologic observations[7b,8,9] and studies in human volunteers provide[5a,6a,7a] strong evidence that at least two agents are concerned. The exact relationship between these two viruses, whether different viruses or different strains of the same virus, remains to be determined. For purposes of reference, the broad terms "virus IH" and "virus SH" are suggested as a tentative aid in avoiding confusion resulting from the lack of specific methods for identification of the viruses concerned. As "virus IH" and "virus SH" each may include one or more

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strains with similar properties, these terms are considered by the author preferable to the more specific and singular implication suggested by the terms "virus A" and "virus B"[7c,10] which have been subsequently suggested by others for reference to "virus IH" and "virus SH," respectively. For the same reason, when characteristic epidemiologic or human volunteers' data are not available concerning one of the hepatitis agents, as often is the case in clinical practice, the broad term of "viral hepatitis" appears preferable.

"Virus IH" (virus A) has been identified primarily with the clinical and epidemiologic syndrome of infectious (epidemic) hepatitis which occurs spontaneously in the form of sporadic cases or epidemics in association with an incubation period varying from two to six weeks. "Virus SH" (virus B) has been associated with the syndrome of hepatitis that characteristically develops one and one-half to six months after the occurrence of an opportunity for parenteral entry of the virus. The epidemiologic term "homologous serum hepatitis" unfortunately has acquired a misleading etiologic implication in that it usually has been employed for reference to the hepatitis syndrome occurring after the long one and one-half to six months' interval. It is emphasized that "virus IH" also may be transmitted by blood or its products and cause "homologous serum hepatitis" after an interval varying between two weeks and two months. Thus syndromes of hepatitis occurring two weeks to six months after exposure to blood or its products may be of viral origin and could justifiably be called "homologous serum hepatitis."

Although the properties of the two hepatitis viruses described above appear to account satisfactorily for most of the viral hepatitis syndromes ordinarily encountered, the possibility remains that other similar strains of hepatitis virus exist. The field epidemiologic studies[7b,8,9] and the experimental studies in human[5a,7a,6a] volunteers that have provided the basis for the distinction between "virus IH (A)" and "virus SH (B)" are summarized in Table 1.

EPIDEMIOLOGY

Human blood and feces are the only proved sources of hepatitis virus and the agents may be present in these materials in very high concentration. Thus 50 cc. of a one to one million dilution of whole blood (0.0001 to 0.00001 cc.) has been shown to be infectious. The viruses apparently may be present in blood or feces in the absence of previous or existing symptoms or signs and the blood or feces carriers may be infectious before, during or after the occurrence of a clinical illness recognizable as hepatitis.[5a,c,6a,7a,12a] The existence of long-term, asymptomatic blood or feces carriers of hepatitis virus with no history of recognized hepatitis recently has been definitely established.[5d,13a] As no host of hepatitis viruses other than man has been recognized, the current concept of epidemiology thus begins and ends with the human host. Either of the recognized viruses may be acquired from human blood but only "virus IH" (A) has been proved to be present in the feces. Neither has been proved to be present in the urine or nasopharyngeal secretions. Most of the naturally acquired infections, sporadic or epidemic, appear to be due to "virus IH" transmitted by the intestinal-oral route by means of food, fomites, water etc. The possible mechanisms of transfer of either of the hepatitis viruses from human blood or its derivatives are multiple. These include transfusion or other injection of human blood, plasma, or serum (or from materials containing or prepared from these substances) and infection from improperly sterilized syringes, needles, lancets or other instruments that have been in contact with human blood. Recently evidence of in utero transmission from an apparently healthy carrier mother to her fetus has been obtained.[13a] This may represent one of the natural modes of transmission of virus (SH) accounting for its survival prior to the "transfusion-needle-syringe era."

With the development by Cohn and coworkers[14] of technics for the fractionation of *human* plasma proteins by the ethanol precipitation method, and with the widespread clinical use of the blood fractions thus produced, the question of whether these fractions might transmit viral hepatitis has assumed great importance. The *gamma globulin fraction*, as prepared by ethyl alcohol (ethanol) precipitation, appears to be free of hepatitis virus, despite the fact that individual lots of gamma globulin (human immune serum globulin) may represent the pooled plasma of thousands of donors.[12b,15,16] It would appear that in the preparation of this fraction by ethyl alcohol the virus is inactivated, eliminated, or neutralized. The *albumin fraction*

prepared in this way after appropriate heating has not been shown to contain the virus, and the albumin solutions as now prepared are apparently safe, due to the fact that this product can withstand the degree of heating required to inactivate the virus.[12c,17,19] Viral hepatitis likewise has not been reported following the use of *antihemophilic globulin*, as prepared by the ethyl alcohol precipitation method.[18] The disease has occurred, however, following the use of *topical thrombin*.[18] It must be emphasized that the above observations apply only to the fractions produced by the ethanol precipitation method and that fractions resulting from other methods of preparation will require re-evaluation and should not automatically be regarded as safe.

The disease now has been recognized as an occupational disease among professional personnel and laboratory workers[20–22] engaged in the handling of blood or its products, and the extent of this hazard has been further recognized by the recent demonstration of virus in the blood of apparently healthy persons.[5d,13a] Although there is no definite evidence of mechanical or biologic transmission of hepatitis virus by biting insects, this possibility must exist whenever an etiologic agent may be transmitted by minute amounts of plasma or blood. The many potential mechanisms for acquiring hepatitis virus from either blood or feces of either obviously infected or apparently healthy persons clearly indicate that a history of contact with an overt case of hepatitis is of little importance as a factor for or against the diagnosis of viral hepatitis in any suspected case.

Both sexes and all races are susceptible to both of the recognized hepatitis viruses. In civilian populations "virus IH" hepatitis occurs predominantly in children and young adults but may occur at any age. A sharp decrease in

TABLE 1

OBSERVED DIFFERENCES BETWEEN TWO HEPATITIS VIRUSES

Source	Observation	Virus IH (or A)	Virus SH (or B)
Observed in human volunteers with experimentally induced infections	1. Usual type of onset	Abrupt; febrile, often high fever; often one chill	Insidious; afebrile or temperature usually less than 100°C.; rarely a chill
	2. Abnormal hepatic tests	Preceded by symptoms for several or more days	Often precede symptoms by several to many days
	3. Thymol and colloidal gold responses	Usually abnormal	Frequently negative or only weakly positive
	4. Usual incubation period (virus entry to clinical onset)	2 to 6 *weeks*	1½ to 6 *months*
	5. Route of inoculation	Clinical hepatitis follows either oral or parenteral entry after 2 to 6 weeks	Clinical hepatitis after parenteral *but not* after *oral* entry
	6. Virus demonstrated in:	Blood and feces	Blood only
	7. (a) Oral ingestion of known infectious serum	Clinical hepatitis	No hepatitis
	(b) Parenteral injection of infectious serum	Clinical h patitis	Clinical hepatitis
	8. Oral ingestion of feces suspensions	Clinical hepatitis	No hepatitis
	9. Resistance to infection (immunity after):		
	(a) virus IH infection	Present	Absent
	(b) virus SH infection	Absent	Present (up to 1 year)
Based on epidemiologic studies	10. Incidence after 30 years of age	Sharp decrease	No apparent decrease
	11. Prevention by prophylactic injections of gamma globulin (human ethanol p'pt.)	Yes	No

incidence, however, is observed in exposed persons over the age of thirty, presumably due to acquired immunity. There apparently is no decrease in susceptibility to "virus SH" infections with advancing age. In fact, this disease probably occurs more frequently in adults because of their more frequent exposure to the mechanisms of transfer of hepatitis virus from blood and its derivatives. Exact incidence figures are not available for either virus although the disease now is reportable in many states. The actual incidence undoubtedly is much greater than that reported because of the frequent lack of recognition of non-icteric cases which may account for as many as 70 per cent of the actual infections.[5c,13a,23] The non-icteric form may be the rule in young children and such unrecognized cases undoubtedly constitute an important source of infection.[5e,24a,b] Epidemics of hepatitis occur annually in both civilian and military groups. In the armed forces of this country acute hepatitis continues to be one of the important medical problems and causes of man-days lost from duty per year.

The usual incubation period of "virus IH" hepatitis apparently ranges from two to six weeks *irrespective of whether the route of entry is oral or parenteral*. Under certain conditions, particularly circumstances leading to attenuation, the incubation period may be prolonged considerably.[5e] The interval between parenteral entry of "virus SH" and the onset of clinically recognizable manifestations usually ranges from one and one-half to six months.

IMMUNITY

Available data indicate that infection with either "virus IH" or "virus SH" apparently is followed by resistance to re-infection with the homologous virus.[5a,6a,8] Although the duration of such resistance has been demonstrated experimentally only for a period slightly longer than one year, epidemiologic and other data suggest that the duration of resistance to re-infection with "virus IH" may be lifelong and similar to that resulting from measles. This is further supported by the protective effect against "virus IH" infections of human immune serum (gamma) globulin prepared by the ethanol fractionation method from the pooled plasma of human adults.[13b,c] The effectiveness of this material in this respect suggests that many persons must have had previous inapparent immunizing infections. Epidemiologic data regarding immunity from "virus SH" infections beyond the period of one year are not available. Available information suggests that this virus may be associated with a peculiar immunologic response as human immune serum globulin and convalescent plasma obtained after "virus SH" infections have failed to protect human volunteers from "virus SH" infections.[12a,25] In addition, a difference in the globulin responses to infection with the two viruses is suggested by the fact that, under experimental conditions in limited numbers of human volunteers, "virus IH" infections uniformly were associated with strongly positive thymol, colloidal gold and zinc turbidity reactions whereas "virus SH" infections frequently were associated with negative responses to all of these tests throughout the course of the infection.[5b,f]

Recently some evidence of active-passive immunization has been obtained in persons who received gamma globulin and who continued to be exposed. Actively immunizing infection presumably occurred but was suppressed to a subclinical level by the gamma globulin.[13c]

Although the evidence seems clear that considerable resistance to re-infection with the same virus exists for one or more years after infections with either "virus IH" or "virus SH," the evidence seems equally clear that no cross immunity between the two viruses exists.[5a,6a,8] In fact, certain epidemiologic data suggest that when equally exposed to one virus (IH or SH), those previously infected with the other virus have a somewhat higher incidence of infection than those without recognized previous infection with the other viruses.[8]

It seems probable that the immune state of blood recipients is of considerable importance in governing the sequence of events following injection of blood or plasma which may contain either or both "virus IH" (A) or "virus SH" (B). MacCallum[7a] recently has emphasized this as essential to an understanding of otherwise apparently conflicting reports on the results of studies of hepatitis in human volunteers. Results that might be observed from infection with the two hepatitis viruses in accordance with the variation in the state of immunity of the recipient are summarized in Table II. The possibility of simultaneous infection of the same person with both hepatitis viruses from a single blood specimen resulting in two separate attacks of jaundice within a six-month period is noteworthy, as the second attack in such a sequence

of events ordinarily might be regarded as a relapse of the initial infection.

CLINICAL MANIFESTATIONS

The variability of the clinical course of viral hepatitis has not been sufficiently emphasized.

TABLE II
RESULTS WHICH MAY BE OBTAINED THEORETICALLY BY INJECTION OF BLOOD FROM PATIENTS WITH VIREMIA (IH OR A; SH OR B)

Virus in Donor's Blood	Immune State of Recipient	Result
A (IH)	O	Short incubation
A (IH)	B	Short incubation
A (IH)	A	No disease
B (SH)	O	Long incubation
B (SH)	A	Long incubation
B (SH)	B	No disease
AB (IH and SH)	O	Short + long incubation
AB	A	Long incubation
AB	B	Short incubation
AB	AB	No disease

O indicates that there is no immunity to hepatitis viruses A (IH) or B (SH). (Adapted from MACCALLUM, F. O. Hepatitis. *Brit. M. Bull.*, 9: 221, 1953.)

The lack of a specific diagnostic test and unfamiliarity with the different clinical variants prevent the recognition of many infections that deviate from the familiar typical pattern of acute hepatitis with jaundice. This is particularly true of the non-icteric forms.

Acute Non-icteric Viral Hepatitis. Although the incidence of non-icteric infections varies with the particular strain of virus and the age group involved, it is believed that non-icteric hepatitis occurs more frequently than hepatitis with jaundice. The *symptoms* of the non-icteric disease are qualitatively similar to those of the icteric form but usually are somewhat less in degree and duration.[5b,6a,23,24,26] In young children the symptoms may be predominantly those of a gastroenteritis or a diarrheal disease.

The *physical findings* may be entirely similar to those of icteric hepatitis except for the absence of overt jaundice. In some, physical findings may be absent. Apparently the non-icteric disease may at times pursue a prolonged chronic course. In some such infections the virus may be present in the blood or stool for long periods, often without the association of noteworthy symptoms.[13a] This non-icteric carrier state undoubtedly represents a dangerous and usually unrecognized source of infection of others.

The results of *laboratory tests* in non-icteric hepatitis may be entirely similar to those subsequently described for the icteric disease except that hyperbilirubinemia is slight or absent. Urine bilirubin occasionally may be detected even in the absence of hyperbilirubinemia. Particularly in the newborn and very young children the results of hepatic tests may be quite variable and often may deviate little from the normal. Lacking a specific diagnostic test and with inconsistent responses of the hepatic tests, it is evident that such infections frequently will not be diagnosed and, except when observed during the course of an epidemic, may not even be suspected. Due to the uncertainty of the diagnosis, more precise description of the variants of the non-icteric infections must await the development of a specific diagnostic test.

Acute Icteric Viral Hepatitis. This is the commonly recognized form of the disease and consists of three stages, namely, the pre-icteric, icteric and post-icteric stages. As this form of the disease is familiar to all,[5b,6a,23,27] no further description herein is warranted.

However, the increasingly frequent recognition of severe viral hepatitis in the newborn, infants and very young children warrants special comment. Recent evidence clearly indicates that the infection may be congenitally acquired from the mother's blood.[13a,28,29] The infection also may be acquired through the usual mechanisms at birth or during the neonatal period in infant nurseries. It is of interest that the mothers, from whom the infants apparently acquired the disease in utero, usually had no history of hepatitis. Likewise no clinical or laboratory evidence of hepatic disturbance was demonstrated in one such mother who was proved to have hepatitis virus in her blood stream by transmission experiments in human volunteers. As the hepatic tests in the newborn and very young infants are not dependable and give variable results in hepatic disease, differential diagnosis may be very difficult.

Although hepatitis in the fetus of a mother who had overt hepatitis during the last month of pregnancy has been observed,[30] hepatitis was not observed in any of the newborn infants in two groups of twenty-nine and fifty-seven mothers, respectively, who had jaundice at sometime during pregnancy.[31,32] At the present time, the available information does not permit

conclusions regarding the relationship of congenital deformities and stillbirths to maternal acute hepatitis during pregnancy. Three children in one series[32] did have brain deformities and approximately 20 per cent of the survivors of another series suffered from varied sequellae including deafness in two and mental retardation in two.[29]

Finally, it appears that young children frequently have a mild form of viral hepatitis with little or no jaundice. This non-icteric disease apparently occurs more often in children under five than in older children. The occurrence of the non-icteric disease in nurseries, often unrecognized in the young children, has been shown to be the source of endemic hepatitis, particularly among the nurses, in several institutions. Such infections may be associated with fecal virus excretion over a period of many months.[13a,24,26]

COMPLICATIONS OF ACUTE VIRAL HEPATITIS

Complete clinical and laboratory recovery from acute viral hepatitis usually occurs within four months. The ultimate outlook for the average infection is excellent although, as compared with most other infections, hepatitis is a disease of relatively long duration and thus of high morbidity. An uncertain number of patients may have one of several variations from the usual course of the disease. Most of the available information pertains to those patients who have had acute viral hepatitis *with* jaundice as the diagnosis frequently is not made in the non-icteric infections. Likewise, most follow-up information has been derived from follow-up studies[5g,33a,b,34a,b,35,36,37a,38a,b,39] carried out on relatively young male adults. However, the incidence of complications may vary with the virus concerned and the age, sex and over-all condition of the patient. For example, hepatitis acquired from blood transfusion in civilian life commonly occurs in the older age groups and the patient concerned often has some other serious associated condition which required blood transfusion. For these reasons, the frequency of complications might be expected to vary under these different circumstances.

The following are among the recognized important complications: (1) Fatal hepatitis; (2) relapsing and/or recurrent viral hepatitis; (3) prolonged hepatitis; (4) chronic hepatitis; (5) the carrier state and (6) other post-hepatitis states, including post-hepatitis syndrome and hyperbilirubinemia.

Fatal Viral Hepatitis. Reported mortality rates for large outbreaks of naturally occurring "virus IH" hepatitis usually range in the neighborhood of 0.2 per cent.[5a,6a,34c] This same rate was observed in the remarkable massive outbreak of "virus SH" hepatitis that followed inoculation of U. S. troops with yellow fever vaccine in 1942.[5h,40] As many unrecognized non-icteric cases probably were not included in the computation, the actual rate for this outbreak probably was lower. In other small localized outbreaks mortality rates following blood or plasma transfusions have ranged as high as 20 per cent.[5c,41] A particularly malignant form of hepatitis with mortality rates varying from 11 to 50 per cent, affecting mainly elderly women, has been observed in the Scandinavian countries but has not been proved to be of viral origin.[42] It is believed that the variations in mortality rate may be influenced by one or more of the following factors: (1) The particular strain of virus concerned, including the conditions under which it has existed prior to patient entry; (2) possibly the size of the infecting dose; (3) the age, general health and immunologic state of the patient (including the presence or absence of pre-existing liver disease or other associated diseases); (4) possibly the management of the patient, particularly during the acute stage of the disease. The above mortality rates, although quite low in most epidemics and other outbreaks, nevertheless result in a disturbingly large number of fatal cases because of the high total incidence of the disease. These rates furthermore do not include the small group of patients dying from advanced liver disease some years after an attack of presumed acute viral hepatitis.

From the clinical point of view, the potentially fatal nature of the disease presents a special problem because the initial course of fatal viral hepatitis may not differ from that of the ordinary mild or average infection. Patients with the mildest initial symptoms may suddenly develop rapidly progressive hepatic failure terminating in death within two to five days. Death in fatal hepatitis may occur at any stage of the disease but most of the fatal infections fall within two main types, namely, the *fulminant* and the *subacute* types.[34d,43a] In the *fulminant* form death usually occurs within ten days of the recognized onset, sometimes before the disease has been

present sufficiently long for jaundice to become apparent. In the *sub-acute form* death usually occurs from three to eight weeks after the onset.[34b,c] In these cases jaundice often has been prolonged or is of the relapsing type. The icteric phase of the disease initially may have followed the customary pattern with no phenomena suggesting the eventual fatal nature of the disease. In others there is a slow gradual increase in the degree of hepatic insufficiency. Eventually a sudden change occurs, often indicated by symptoms referable to the central nervous system including personality changes, stupor, delirium or occasionally convulsions. Fever and leukocytosis commonly occur in association with the changes in symptoms which also include persistent vomiting, the development of ascites, edema, hemorrhagic phenomena and eventually coma. Coma may develop suddenly or may follow gradually increasing stupor. Occasionally symptoms due to hypoglycemia, hypocalcemia or electrolyte disturbances may confuse the picture. These factors are important in therapy.

As will be mentioned in the next section, a few patients may survive one to many years with chronic latent or active hepatitis until gradually increasing hepatic insufficiency or other complications of chronic liver disease, such as portal hypertension, lead to death.

Recurrent and/or Relapsing Hepatitis. The literature is confusing in respect to the incidence of recurrence or relapse of acute viral hepatitis, particularly when this occurs after an interval of apparent recovery following the initial acute episode. Exacerbations of liver disturbance occurring *before* clinical and/or laboratory recovery from the initial attack probably are true relapses and apparently occur in 15 to 25 per cent of patients, even when under close supervision and management.[5c,23,33b,35,44] Such relapses may be a duplication of the original attack or actually may be more severe and even progress to a fatal termination. More often, however, relapses are evidenced only by mild aggravation of the degree of hepatic disturbance revealed by hepatic tests. Relapses occur most often at the time when the patient is allowed to return to physical activity. The duration of the relapse may be short or may extend beyond the period of the initial acute episode. Although relapse prolongs the duration of the disease, most patients ultimately achieve a complete recovery within one year. Available data suggest that only approximately 5 per cent of patients that have relapses fail to achieve an apparent recovery within that period.

When another episode of acute liver disease follows apparent recovery from an initial attack of acute viral hepatitis, the relationship of the second episode to the first becomes less certain with the passage of time.[5d] Thus most *true* relapses probably occur within six months of the initial attack and the clinician must be alert to the possibility of some other cause of the second episode at all times. Thus in persons with two separate attacks of jaundice separated by several months, there is the additional possibility that the first episode represented an "IH" infection and the second an "SH" infection. It is theoretically possible that both of these viruses might be transmitted to the same person by the same blood transfusion or blood product. When the patient is first seen during the second attack, there always is a question of the diagnosis during the first attack. Thus one occasionally finds that the diagnosis was erroneous for the first attack and that one is dealing with multiple attacks of jaundice due to extrahepatic biliary obstruction or occasionally to serum hepatitis following transfusion given during the course of an operation for post-hepatic obstruction. The author has observed a patient with known acute "virus IH" hepatitis who, six months later, developed a second attack of jaundice proved to be due to infectious mononucleosis. It seems likely that second episodes, representing an exacerbation of the initial disease, will usually occur during the early months after the subsidence of the first acute episode. One should be very cautious about attributing second attacks of jaundice occurring after six to twelve asymptomatic months to an exacerbation of the original infection. On the other hand, apparent recovery following an initial attack cannot be safely judged on the basis of clinical observation alone. Thus complete recovery should be based on clinical judgment supported by proof of laboratory recovery as well. Unfortunately, most patients with acute hepatitis observed in civilian practice are discharged as recovered on the basis of the subsidence of the jaundice and clinical symptoms without adequate laboratory follow-up.

Prolonged Hepatitis. This term is used herein for those infections in which clinical and/or laboratory evidence of active hepatic disease persists continuously for more than four months, but from which apparent complete recovery

ultimately occurs, usually within eighteen months. Such infections have been referred to by others as "chronic hepatitis."[44] It seems preferable to the author, however, to distinguish those patients who ultimately recover completely after a prolonged course from those who do not. A number of the infections included under the group designated as "relapsing hepatitis" also could be classified as "prolonged hepatitis." However, it again seems desirable to separate those infections in which the disease is continuous from those in which the course is marked by one or more distinct attacks of uncertain relationship and between which there is an apparent recovery. The available data, which refer mainly to acute hepatitis with jaundice in adult males of military age, suggest that 15 to 20 per cent of the acute icteric infections will fall into the category of "prolonged hepatitis" as defined above. However, the incidence of prolonged hepatitis may be higher in other groups, possibly varying with the same factors that influence mortality (see "Fatal Hepatitis").

In three groups of patients with prolonged hepatitis for which adequate follow-up data are available, approximately 5 per cent failed to achieve an apparent complete clinical and laboratory recovery by the end of one year.[5b,c,33a,b,44] During this interval the trend was usually one of slow gradual improvement at varying rates, the manifestations obviously varying with the time of observation. The findings in general were those associated either with a prolongation of the icteric and/or the post-icteric stages of the acute disease. Among those exhibiting a prolonged icteric phase a few present certain features that differ from the usual course in their laboratory and, to a lesser degree, in their clinical manifestations. In these patients moderate to severe jaundice may persist for months in spite of relative well being of the patient. Pruritus and easy fatigue with ordinary exertion may be the dominant symptoms except for the jaundice. The hepatic tests often are identical with those of post-hepatic obstructive jaundice, namely, negative or variable flocculation tests in association with moderate to marked elevations of alkaline phosphatase and serum cholesterol. Differentiation of these infections from the surgical types of jaundice often is extremely difficult on the basis of clinical or laboratory evidence and needle biopsy of the liver may, at times, fail to make a reliable distinction. The term "cholangiolitic" hepatitis has been applied to this syndrome.[45a,b] As histologic evidence of cholangiolar disease is not recognized in these cases, some have objected to this term. In fact, many pathologists state that they are unable to recognize any difference between this form of hepatitis and the usual clinical form on histologic grounds alone. Nevertheless, there is no doubt that this form of the disease exists as a clinical and laboratory entity in which the phenomena are primarily those of extra- or intrahepatic obstruction. It has been suggested, however, that the process may cause a disturbance in excretion and absorption across the biliary epithelial membranes rather than intrahepatic obstruction. Although some patients with this form of the disease recover completely after a prolonged icteric course, the process in others develops into the chronic hepatic disease which has been referred to as "cholangiolitic cirrhosis."[45a,b,46] Although the clinical and laboratory phenomena tend to follow the course of either the usual or the cholangiolitic forms from the onset of the disease, the phenomena of the latter occasionally may develop during the icteric stage of the former.

Chronic Viral Hepatitis. This term will be used herein for the remaining small group of patients in whom clinical and/or laboratory evidences of liver disease persist continuously for more than one year after the initial onset of viral hepatitis. The degree of hepatic disturbance may vary but persists continuously in clinical or subclinical form, with or without jaundice. It is believed that some such infections, with active disease persisting for several or more years, eventually may resolve in a clinical and hepatic functional recovery. However, inadequate clinical or hepatic histologic studies of a group of such patients are available to determine if these patients actually have a healed or only a temporarily quiescent disease. More often, the patients of this group gradually suffer a progressive liver injury, with increasing hepatic insufficiency, which eventually leads to death from the latter or one of the complications of chronic liver disease. The frequency with which the chronic form develops, as herein defined, can only be roughly approximated. Again the available data refer only to the follow-up studies of young men of military age and do not include non-icteric cases. The actual incidence thus may be quite different with particularly virulent strains and in hosts of different age groups with different associated conditions and states of

general health. Based on the available data, it would appear that approximately 3 to 5 per cent of those who suffer from "prolonged hepatitis" may develop the chronic disease as defined above. This would represent an approximate incidence of only 0.6 per cent of the acute infections originally associated with jaundice. The author has been impressed with the number of persons with advanced chronic disease of the liver, representing some form of chronic hepatitis, who do not have a preceding history of a typical acute attack with jaundice, but who have been known to have a prolonged period of a non-icteric hepatic disease, which resembles that observed in *prolonged non-icteric hepatitis*. In fact, in his own practice, this type of chronic disease is encountered more commonly than chronic hepatic disease following an acute attack initially associated with jaundice. Until the etiology of this chronic liver disease preceded by a long non-icteric phase without an original acute icteric attack is clarified, it is difficult to be certain whether the low incidence of chronic hepatitis following recognized attacks with jaundice may not misrepresent the true incidence of chronic disease resulting from viral hepatitis.

The clinical and laboratory phenomena of chronic hepatitis are similar to those of other chronic liver diseases and cirrhosis. Physical findings may include spider nevi, palmar erythema, ascites and edema, gynecomastia, hepatomegaly with or without splenomegaly, splenomegaly with or without hepatomegaly, with or without jaundice. Evidences of portal hypertension may or may not be present. The phenomena of hypersplenism occasionally may be observed.

The type of morphologic change in the liver apparently is variable.[33a,36,37a,38a,39,43a,b,45b,47,48,49] Death usually occurs either from hepatic insufficiency or from one of the complications of portal hypertension. The liver at postmortem apparently most often presents the change described as post-necrotic cirrhosis. In others, the picture has been described as multiple nodular hyperplasia or as that of portal cirrhosis. Those patients who have had the so-called "cholangiolitic" form of the disease may present the picture of primary biliary cirrhosis.[46]

Although the occasional transition of viral hepatitis into one or the other above mentioned forms of cirrhosis seems well substantiated, the infrequency of this occurrence deserves emphasis. In fact, recent comprehensive follow-up studies of veterans living in different sections of the United States after discharge from military service, made four to eight years after a previous attack of acute viral hepatitis with jaundice, indicate that the incidence of chronic hepatic disease is no greater in this group than in a group of controls without a history of acute hepatitis with jaundice.[5g,39] During their extensive studies of postmortem material during World War II, Lucké and Mallory[34,43a,b] likewise were unable to establish any consistent association between cirrhosis and previous hepatitis. However, most of their studies were concerned with fulminant and subacute fatal hepatitis. In other words, although cirrhosis apparently may follow an attack of hepatitis, the available data suggest that cirrhosis is no more frequent in persons who have had hepatitis four to eight years previously than in those who have not had recognized hepatitis. All of the above studies are subject to certain limitations which prevent their acceptance as conclusive evidence of the lack of a relationship between cirrhosis and antecedent hepatitis. In the first place, these studies were limited in respect to age and sex, dealing largely with males of military age. Secondly, they were concerned almost exclusively with the end results of acute hepatitis with jaundice. As mentioned earlier, many patients encountered in clinical practice with advanced liver disease, that must now be classified as chronic hepatitis and cirrhosis of unknown etiology, have had a non-icteric disease of long duration before clinical manifestations or medical examination leads to demonstration of the presence of this disease. Thus the exact relationship between an acute viral hepatitis, icteric or non-icteric, and cirrhosis must await the results of further study after a specific diagnostic test becomes available. Perhaps supporting the possible significance of non-icteric hepatitis as an etiologic factor of importance in the development of hepatic cirrhosis is the recent demonstration of several relatively asymptomatic persons with hepatic cirrhosis, with no antecedent history of hepatitis, who have been shown to be long-term blood carriers of hepatitis virus.[5d] In these persons other factors, such as alcoholism, may have contributed to the hepatic cirrhosis but the presence of hepatitis virus in the blood stream over long periods would appear to be more than coincidental.

The Carrier State. During the last several years conclusive evidence has been obtained that

long-term blood and fecal carriers of hepatitis virus exist.[5d,13a] The majority of the proved carriers have had no history of previous acute hepatitis with jaundice. Likewise the majority have had no specific symptoms or conclusive physical findings. Although most of the proved carriers have had some evidence of hepatic disturbance demonstrable by hepatic tests and several have had evidence of advanced liver disease demonstrated by liver biopsy, others have been entirely free of symptoms and of hepatic abnormalities as demonstrated by laboratory tests. In this last group, unfortunately, liver biopsies have not been available. One such carrier was a young mother whose newborn infant developed hepatitis suggesting the possibility of in utero transmission. The carrier state of the mother in this instance was demonstrated by transmission experiments in human volunteers.[13a] Further clarification of this state must again await development of specific diagnostic tests other than human volunteer method.

Other Post-hepatitis States. Attention also has been directed to a small group of patients who continue to have subjective complaints of anorexia, fatigue, abdominal discomfort and various non-specific gastrointestinal symptoms for prolonged periods after apparent recovery from acute hepatitis.[38b,50] The term "post-hepatitis syndrome" has been applied to this condition in which other objective evidences of continued hepatic disturbance, including needle biopsy of the liver, cannot be demonstrated. It is believed that the symptoms of these patients are on a psychosomatic basis. Frequently a reason, such as loss of a pension or other convenience of illness, accounts for the need of continued symptoms in such patients. This diagnosis, however, should not be made without proof of normal liver histology as it has been demonstrated that active hepatic disease may be present in the absence of other laboratory evidence of hepatic disturbance.

Finally, the syndrome of so-called *constitutional or familial hyperbilirubinemia*[45c,51] deserves mention. This condition is characterized by an elevation of the indirectly reacting serum bilirubin and normal hepatic function as measured by all other available tests, and without evidence of hemolysis or other known mechanisms of hyperbilirubinemia. Liver biopsy in such patients apparently reveals what is considered to be normal morphology. Patients with this syndrome frequently are asymptomatic. Others have occasional periods of vague and non-specific symptoms which vary with fluctuation in the level of the serum bilirubin but with no other demonstrable evidence of active disease. In a few such patients functional hypoglycemia is the cause of such symptoms and may be part of the syndrome. Although this syndrome has been observed in patients who have had a definite history of previous acute viral hepatitis with jaundice, it frequently is observed in persons without such history. It seems possible that those who are observed with this syndrome after viral hepatitis may have had this condition prior to the attack of viral hepatitis. At the present time a relationship between the two cannot be confirmed or denied and further clarification again must await the development of specific diagnostic tests.

DIAGNOSIS

As previously mentioned, specific diagnostic tests for viral hepatitis have not been developed. The diagnosis thus depends mainly on clinical and epidemiologic evidence, the pattern of response of certain non-specific laboratory procedures, and the exclusion of other diseases. The presenting problem usually is the establishment of the condition as one of the types of viral hepatitis or the sequellae. The conditions from which this disease must be differentiated vary according to the stage of the disease.

During the *pre-icteric stage* or in *non-icteric* hepatitis the manifestations may simulate those of a variety of acute infectious diseases, those of an acute condition within the abdomen or those of any one of the gastroenteric disorders. This great variability in the type of onset of viral hepatitis requires constant consideration if errors in diagnosis are to be avoided. It is for this reason that the diagnosis of viral hepatitis usually is not made until jaundice appears, which may be several weeks after the onset of symptoms. During this *early* stage tenderness or pain in the hepatic area should arouse suspicion. These symptoms frequently are absent, however, as are other local manifestations pointing toward the liver or biliary tract. In such cases, the diagnosis may be suspected by the alert clinician from the application of a group of hepatic studies. The daily inspection of a urine specimen often would suffice. Except for this, the most useful tests at this stage are the bromsulfalein excretion test, the determination of bilirubin and uro-

bilinogen in the urine, measurement of the serum bilirubin (total and prompt direct reacting) concentration and the flocculation tests. Although positive results with any of these tests will not *establish* the diagnosis of viral hepatitis, they may provide an important clue, at least, that should narrow the field of diagnostic possibilities. The absence of a history of contact has no value in excluding the diagnosis of viral hepatitis because of the many potential sources of infection described in the section on epidemiology.

The problem in diagnosis during the *icteric stage* is essentially that of the differential diagnosis of jaundice which does not fall within the scope of this article. It is emphasized that the *age* of the patient affords little evidence for or against the diagnosis. Viral hepatitis is the most frequent cause of jaundice (other than in the newborn) in children and young adults. The susceptibility of persons in the older age groups to "virus SH" and their frequent exposure to the mechanisms by which this virus may be acquired from blood, perhaps together with a greater distribution of the hepatitis viruses among the general population, have resulted in the frequent occurrences of viral hepatitis in these older age groups. This creates a particular diagnostic problem with "virus SH" hepatitis, the onset of which often is that of a relatively insidious, progressively developing jaundice. This mimics the textbook picture of malignant post-hepatic obstruction of the biliary tract. The diagnosis of viral hepatitis thus must be seriously considered regardless of age. Its recognition is particularly important since patients with viral hepatitis often tolerate surgery poorly, the risk associated with surgery being considerably greater (although less today than in the past) than that associated with operations for jaundice of post-hepatic obstructive origin. It is likewise desirable to avoid undue delay in the exploration of patients with post-hepatic obstructive (non-receding) jaundice. However, if bacterial cholangitis is absent, such patients rarely suffer from a period of "watchful waiting," often an important aid in the diagnosis.

The differential diagnosis, therefore, of "surgical" and "medical" jaundice is of importance and viral hepatitis, at times, offers considerable difficulty in this respect. The presence of strongly positive cephalin cholesterol and thymol tests during the early weeks of jaundice affords evidence in favor of an intrahepatic cause of jaundice. If the jaundice is severe, a normal or only slightly elevated alkaline phosphatase activity is more consistent with an intrahepatic than with a post-hepatic obstructive cause. Under the same circumstances, normal total serum cholesterol, with a marked decrease in the quantity of esterified cholesterol, is more consistent with an intrahepatic, than a post-hepatic obstructive cause. Unfortunately, an important element of intrahepatic obstruction (or disturbance of the biliary epithelial absorption-regurgitation mechanism) frequently occurs during the course of hepatitis and other types of intrahepatic disease. In such cases the presence of an increased alkaline phosphatase activity and a high total cholesterol concentration may falsely suggest the presence of a post-hepatic obstruction. Also, one or more of the flocculation tests may be negative throughout the course of hepatitis (20 per cent of cases),[5i] further complicating the picture. In these instances needle biopsy of the liver may or may not be of value in determining whether the cause of the jaundice is intrahepatic or post-hepatic in origin. Although the jaundice eventually may be proved to be of hepatic origin, it must be admitted that the diagnosis of viral hepatitis often remains presumptive and that many such cases actually may be of toxic or other origin.

During the *post-icteric stage* the persistence of vague symptoms including weakness, malaise and vague gastrointestinal complaints may be responsible for sufficient disability to require special study and management. In some persons these symptoms may be the result of other conditions that existed prior to, or developed during the course of or following the attack of acute hepatitis. Careful and detailed study may be necessary to identify properly the cause. Differentiation is essential as proper management in one type of hepatic disturbance may affect adversely symptoms from another source, for example, those of psychosomatic origin. The greatest assistance in the diagnosis of the role of viral hepatitis in these conditions again comes from the laboratory. The tests of most value for revealing the existence of mild degrees of subclinical hepatic disease are the bromsulfalein excretion test, the test for urinary urobilinogen (preferably the quantitative extraction method applied to a twenty-four hour specimen), measurement of the total and prompt direct reacting serum bilirubin, and the cephalin-cholesterol flocculation, thymol turbidity and

flocculation tests, and zinc turbidity test. When evidence of hepatic disturbance is obtained, it must be realized that this is not specific for *viral* hepatitis. When such symptoms persist for prolonged periods or are detected in patients with a prior history of viral hepatitis, one is not necessarily justified in assuming that the condition results from the viral hepatitis.[5g] Other medical conditions associated with hepatic disturbance require exclusion and biopsy of the liver often is essential. In the author's experience some other cause of the symptoms, particularly pain, has been found frequently.

Since recent studies have shown that significant morphologic alterations in the liver may be present in association with minimal or no detectable biochemical evidence of hepatic dysfunction, needle or other biopsy of the liver frequently is essential to the proper clarification of the nature of these conditions.

Finally, a relationship of viral hepatitis to certain chronic diseases of the liver has been suggested. At the present time, the nature of this relationship is obscure. In addition to establishing the diagnosis in order to make certain that chronic jaundice with hepatomegaly and/or splenomegaly is not secondary to undiagnosed lesions of the extrahepatic biliary tract, clarification of the nature of the process is essential to the selection of the proper type of treatment. Needle biopsy of the liver, extensive x-ray and laboratory study or exploratory laparotomy may be required to solve the problem.

The development of newer technics in x-ray examination of the biliary tract offers promise of additional assistance with some of these puzzling problems. Preliminary results with a new intravenous contrast medium, *biligrafin*, has indicated that visualization of the extrahepatic biliary passages frequently is possible in many non-icteric and some icteric cases.[52] Thus the exclusion of obstructive lesions of the posthepatic biliary tract may be possible more often than in the past. When properly trained personnel are available, the technic of direct cholecystography and cholangiography, in conjunction with the peritoneoscopic examination, is useful.[53] In spite of the application of all diagnostic measures mentioned, the establishment of an accurate diagnosis may not be possible in certain patients. In these instances exploratory laparotomy may be necessary if the question of an obstructive lesion of the extrahepatic biliary tract cannot be excluded.

PREVENTION

Prevention of viral hepatitis is particularly difficult because of the lack of methods for recognition of virus carriers, the many potential methods of transmission and the unusual resistance of the hepatitis viruses to many procedures that eliminate, inactivate or destroy most pathogens.

Prevention of the spread of hepatitis viruses involves the consideration of every person as a potential carrier. The proved sources of hepatitis viruses are feces and blood. The prevention of the spread of infection from feces involves all of the common measures associated with the control of the common intestinal pathogens.

Prevention of the spread of hepatitis viruses in blood has raised many new problems. As the presence of hepatitis viruses in the blood cannot be demonstrated other than by transmission experiments in human volunteers and, up to date, no method for inactivation of the virus in blood is available, the use of whole blood or plasma for transfusion continues to be associated with the risk of viral hepatitis.[41] The recent demonstration of asymptomatic blood carriers, without history of previous viral hepatitis with jaundice, is of particular importance in this respect.[5d,13a] Ultraviolet irradiation has not proved to be dependable as a method for inactivation of hepatitis virus in plasma and none of the chemical methods of sterilization of blood or plasma proposed to date has been proved to be satisfactory or dependable although several promising agents are being explored.[4,10,11,12,54] Storage of plasma in the liquid state (not dried) at room temperature six months or longer may be associated with a decrease in incidence of the disease.[12d,55] However, this method is not applicable to whole blood and is cumbersome as a method for the treatment of plasma. Storage at room temperature for three months in the liquid state has been shown to be ineffective for the inactivation of hepatitis virus.[12d] At the present time (1954), therefore, there is no entirely satisfactory method for the elimination of hepatitis virus from whole blood or its products other than albumin and gamma globulin (as now prepared). For this reason, whole blood, plasma and the blood products, other than albumin and gamma globulin, should not be used unless the indications outweigh the risks of a potential attack of viral hepatitis. In evaluating this, it appears that the risk increases proportionately with the

number of units of plasma involved. Recent studies indicate that ultraviolet irradiated pooled plasma, as prepared by commercial processes, is associated with a 12.8 per cent incidence of hepatitis.[41] Thus pooled plasma, or multiple single transfusions, will be associated with a higher risk than with the use of single blood transfusions, the latter being associated with approximately a 0.5 to 1.5 per cent incidence. No reliable data are available concerning the incidence of carriers of hepatitis virus. Existing information suggests, however, that blood carriers among the donor population, in some areas at least, may range between 1 and 5 per cent. This figure might be higher if transient asymptomatic carriers are included. Prevention of transmission by this means thus can best be accomplished by the avoidance of the use of such blood or its products unless necessary. Recent studies have suggested that a high percentage of asymptomatic blood carriers of hepatitis virus may have detectable evidence of hepatic disturbances as indicated by hepatic tests.[56] Approximately 10 per cent of random blood donors exhibit a significant abnormality with one or more of a group of sensitive hepatic tests (total and one-minute serum bilirubin, bromsulfalein, zinc turbidity, thymol turbidity and flocculation, urine urobilinogen). As the hepatic abnormality in most of the proved, infectious, asymptomatic donors was reflected by abnormal thymol and zinc turbidity tests, it is probable that a significant number of potentially infectious donors could be excluded if these tests were performed routinely on all blood donors in the same fashion as the routine culture and the serologic test for syphilis. Such methods will not eliminate the problem of blood-transmitted hepatitis but possibly may aid in a reduction of the incidence.

Unfortunately, the development of satisfactory methods for inactivation of hepatitis virus in blood and its derivatives will not eliminate all of the problems associated with the transmission of these viruses from blood. The other mechanisms of transmission associated with the use of improperly sterilized needles, syringes, lancets and other instruments coming in contact with blood or its products will remain as sources of infection. Elimination of these methods of transmission involves the use of adequately sterilized instruments for each patient. This applies to instruments used for such routine procedures as blood counts and needles and syringes used for simple venipuncture or injections. The minimal procedures necessary to disinfect adequately such instruments have not been accurately determined. Simple rinsing and immersion in alcohol or other disinfectants has not proved to be dependable. This perhaps may be largely a matter of the undependability of technics performed by human beings. Thus adequate exposure to proper chemical disinfectants for a sufficient length of time undoubtedly is capable of disinfecting hepatitis virus. However, the information necessary to establish the minimal requirements is not available. For this reason, adequate sterilization of such instruments requires, at the present time, thorough cleansing of all instruments to insure removal of all traces of foreign material such as blood clots, followed either by boiling, autoclaving or, when appropriate, flaming.

"Virus SH" has not been infective when administered by the oral route and the stools from patients with "virus SH" infections have not been shown to be infectious (most such studies have involved inoculation by the oral route and, as this virus appears to be infective only by the parenteral route, the absence of this virus in the stools has not yet been adequately proved). Patients known to have this infection ordinarily would not require isolation. Unfortunately, in most sporadic cases of viral hepatitis it is not possible to be absolutely certain whether "virus IH" or "virus SH" is concerned. It is necessary, therefore, to assume that both the stool and the blood are infectious in the management of most patients with this disease. Although the virus apparently does not spread easily or rapidly through hospital wards, this and spread through a family occasionally do occur. The high morbidity and occasional mortality thus require that infectious precautions be instituted in the management of such patients whenever feasible. In most families, other members of the family usually have had maximal exposure by the time that the diagnosis is made, and institution of strict infectious precautions then probably is useless. All those in contact with the patient should be instructed to wash their hands thoroughly with soap, preferably followed by a disinfectant, after handling any article that may have come in contact with the patient. Hospitalized patients ideally should be placed under infectious precautions similar to those instituted for other infectious enteric diseases plus the general measures taken to avoid transmission from blood.

In this respect particular care should be exerted in the handling of patients with colostomies or open lesions associated with the oozing of blood or serum. As many of the patients with viral hepatitis are surgical patients, contact with such materials is common among these involved with dressing of wounds.

"Virus IH" infections can be prevented by the intramuscular injection of normal human serum globulin in a dosage of 0.02 cc. per kg. of body weight if administered prior to the onset of symptoms and signs of the active disease.[6b,12b,13b,c] If such gamma globulin is available, it should be given routinely to all those exposed in the course of a spreading epidemic, to those exposed heavily to individual cases and to those accidentally receiving unusual exposure by other mechanisms. Although such gamma globulin apparently does not protect against "virus SH" infections,[25] one often is not certain about the type of infection concerned in individual patients. Supplies permitting, prophylactic injections of gamma globulin would be desirable in all patients receiving multiple blood transfusions.

There is some evidence to suggest that those injected with gamma globulin, who continue to be exposed and are infected by hepatitis virus during the period of passive protection, may actually benefit from a so-called "active-passive" immunization resulting in prolonged immunity.[13a,24]

TREATMENT

Although no specific treatment for viral hepatitis is available, the natural tendency of the disease is toward spontaneous recovery. Thus most patients will recover fully and completely with no treatment other than restriction of physical activity during the active stages of the disease and a high caloric, high protein, high carbohydrate, moderate fat diet. Unfortunately, the disease is unpredictable and it is not possible to determine, at the onset, which infection may be fatal or may be followed by one of the other variants from the usual course of prompt and spontaneous recovery. Thus it is necessary to treat all patients with hepatitis initially for a potentially fatal or serious disease until proved otherwise. Because of the great variability of the course of the disease, it is impossible to outline a standard treatment program. The basic principles of treatment are restriction of physical activity and diet.[5j,23,44]

The concepts concerning the degree of restriction of physical activity are undergoing some change as the result of recent studies in U.S. Army troops in Korea.[57,58] Based on these studies a Committee on Hepatitis of the Commission on Liver Disease of the Armed Forces Epidemiological Board has issued[57] the following statement regarding the treatment of *uncomplicated* acute viral hepatitis:

"The following recommendations for the treatment of acute infectious hepatitis are general principles and may require modification for the individual patients under particular circumstances. They embody a distinct change in the presently accepted rest regimen and little or no change in dietary treatment. They are based on the conclusions of a carefully controlled study of enlisted military personnel with acute infectious hepatitis. Their applicability to the more severe forms of the disease in older or less well nourished patients has not been established.

"Since physical activity to the point of fatigue may be harmful, patients with acute hepatitis should be hospitalized as soon as the diagnosis is made. They should be urged to rest in bed as long as acute symptoms persist. Once they begin to feel well, regardless of the degree of jaundice, they should not be forced to stay in bed more than an hour after each meal. Restriction to the hospital ward, however, is essential to decrease undue activity or exertion. Allowing ad lib activity on the ward (without any required exertion) circumvents the usual delay necessary for recuperation from the effects of prolonged rest in bed and appreciably shortens the period of hospitalization.

"Patients so treated may be discharged from the hospital and physical reconditioning may be undertaken after the total serum bilirubin is below 1.5 mg. per 100 ml. and the bromsulfalein retention in 45 minutes below 6 per cent for a period of not less than one week. Patients whose bromsulfalein retention stabilizes between 5 and 10 per cent may be discharged from the hospital with safety. Those with persistently higher levels will require individual management.

"Following discharge from the hospital it is well to follow all patients for two weeks with weekly physical examination, serum bilirubins and bromsulfalein tests. Recurrent abnormalities will occur rarely and are probably indications for rehospitalization.

"The optimal diet in the treatment of infectious hepatitis consists of about 3,000 calories

containing approximately 150 gm. each of protein and fat. Intakes above this level should be ad lib. Although fried and greasy foods may cause indigestion, the fat contained in meat, eggs and dairy products is not harmful and adds greatly to the palatability of the diet. During the stage of severe anorexia the patient should be urged to take frequent small feedings. Intravenous glucose solutions should be administered when necessary to maintain a minimal caloric and fluid intake. Although the forcing of a high-protein, high-fat diet, by stomach tube if necessary, has been demonstrated to hasten recovery in the average infection, critically ill patients with fulminating disease or impending hepatic coma may be harmed by excess dietary protein.[59] In these few patients, therefore, it is probably unwise to administer more than a maintenance quantity of protein.

"Intravenous protein hydrolysates, plasma or blood transfusions have no place in the nutritional therapy of patients with uncomplicated infectious hepatitis."

Transfer of these principles of therapy for the management for acute viral hepatitis in military service to the treatment of patients encountered in civilian practice must be modified by discretion. When the disease is acquired by persons of older age groups with other associated diseases, bed rest probably should be maintained until the descending icteric phase is well established and the patient is completely asymptomatic. Also, the resumption of physical activity probably should be carried out more cautiously and with closer follow-up supervision.

The symptoms of acute viral hepatitis are most prominent during the pre-icteric and early icteric phases. Anorexia often is severe and may be associated with troublesome nausea. Until this stage is passed, daily intravenous infusions of 10 per cent glucose with vitamin supplementation is desirable. For nausea, the use of benadryl, pyribenzamine or dramamine in doses of 50 mg. before the main meals may be very helpful. The mild sedative action of benadryl taken at bedtime may promote rest. The use of vitamin B_{12} has been considered beneficial by some. If the nutritional status prior to the onset of hepatitis has been satisfactory and prolonged dietary inadequacy does not occur during the early stage of the disease, there is no definite evidence that the use of the lipotropic agents such as methionine and choline is beneficial. If there is doubt about the prior or present nutritional status of the patient, the author often prescribes methionine in a dosage of 1 to 3 gm. daily until the patient is capable of taking the recommended diet. Appropriate measures to avoid colon stasis also are advisable.

The treatment of *relapse* should include resumption of those measures employed during the initial active symptomatic phase of the disease including bed rest. Present available information suggests the possibility that a relapse may prove to be an indication for treatment with cortisone or ACTH. In addition, patients with tendency to relapse should have a thorough medical evaluation to exclude the presence of associated conditions such as other intestinal infections, including amebiasis, or an incorrect original diagnosis. Any such conditions should be appropriately treated unless the indicated treatment is likely to be more hepatotoxic than the condition itself.

In some patients who fail to recover progressively, treatment with one of the broad-spectrum antibiotics such as aureomycin in a dosage of 250 to 500 mg. four times daily for two to four weeks may aid in initiating recovery if such therapy otherwise is well tolerated.[60]

A few patients will continue to have weakly positive hepatic tests for prolonged periods in spite of the absence of symptoms and significant physical findings. In such patients who fail to exhibit progressive improvement on conservative therapy, a cautious trial of increased physical activity with laboratory follow-up of the effect may be necessary.

A decision as to when it is safe to resume physical activity following hepatitis often is difficult as there are no standard objective criteria that may be employed. Under the treatment program outlined above for military personnel, most patients will be ambulatory by the time the serum bilirubin returns to normal. Before any further increase in activity is permitted, the bromsulfalein retention should be 8 per cent or less at forty-five minutes and the thymol and cephalin flocculation tests no more than weakly positive. Likewise the liver should no longer be grossly enlarged or tender. Under these circumstances a very gradual increase in physical activity, beginning with short walks, may be permitted and increased progressively. The remaining abnormal laboratory tests should be repeated one week after such increase in activity. The occurrence of any adverse symptoms such as persistent fatigue without exertion

or gastrointestinal symptoms should lead to prompt re-evaluation. Allowance must be made for the occurrence of fatigue with increasing exertion which may be the result only of the prolonged period of physical inactivity. When the amount of physical activity that ordinarily is involved in one's usual occupation is reached, resumption of work may be permitted. It is desirable, particularly for those who are employed by others and are unable to control their time, to recommend that only half time work be undertaken during the first week. If this is well tolerated, full time work may be resumed. Alcoholic beverages, prohibited until this time, probably may be safely used in *minimal* quantities after all of the hepatic tests have returned to normal. Unusual stress, strain and fatigue should be avoided for a six-month period following acute hepatitis. Routine laboratory follow-up study after three and six months and one year is advisable.

Other general principles of treatment include the institution of infectious precautions for hospitalized patients and the administration of human immune serum globulin to those persons who have been heavily exposed (see Prevention).

Consideration of the *role of cortisone and ACTH* in the treatment of viral hepatitis has been deferred until now because it is believed that the use of these agents is inadvisable in the usual forms of hepatitis which tend progressively toward spontaneous recovery. Evidence available to date, however, indicates that the proper use of these agents when other stronger contraindications do not exist, affects favorably the course of viral hepatitis.[6c,24,37b,61–64] The influence on the average spontaneously recovering infection, however, apparently is not sufficient to justify routine use because of the incidence of adverse effects from these drugs. However, in those infections which are unusually severe, in those with delayed recovery or relapse, in the cholangiolitic types with prolonged jaundice and probably in the early chronic forms the use of these agents appear to be capable at times of initiating progressive recovery. The dosage has not yet been well established and it appears probable that different dosage schedules may be indicated according to the type of complication of viral hepatitis that is being treated. It appears to be generally agreed that cortisone or ACTH therapy should not be initiated unless it is intended to continue such therapy until maximum improvement has been obtained. Thus premature discontinuation of such treatment seems to have been associated with a tendency to relapse. It appears that the cholangiolitic forms with prolonged jaundice and those with delayed recovery will obtain a favorable result with relatively small doses ranging from 20 to 50 mg. of oral cortisone daily after three to ten days of somewhat higher dosage initially. Recently it has been suggested that massive dosage in the order of 600 to 1,000 mg. of cortisone daily is beneficial in the fulminant form with pre-coma or hepatic coma.[62] Sufficient data are not yet available to confirm the preliminary observations in this respect. It is the author's opinion, from his personal experience to date, that cortisone and ACTH are capable of favorably influencing the course of complicated forms of viral hepatitis.

However, only further study will delineate the exact types which will be benefited and clarify the dosage schedule required. When these agents are used, the same precautions employed in their use in other conditions must be followed. Thus salt restriction may be necessary, potassium supplementation indicated and a careful daily search for possible adverse effects carried out. Before using these drugs a careful historical inquiry and a gastrointestinal series is desirable to eliminate those patients who may have an associated peptic ulcer, particularly if the indication for the use of cortisone is not such that heroic therapy, regardless of risk, can be justified. Careful electrolyte control is essential in these patients.

SUMMARY

Available information concerning the etiology and epidemiology of viral hepatitis, including both infectious hepatitis and homologous serum hepatitis, is reviewed and evaluated. The clinical manifestations of the disease are considered primarily in respect to those infections which present problems in diagnosis and/or which deviate from the usual course of prompt and spontaneous recovery. These include fatal hepatitis, recurrent and/or relapsing hepatitis, prolonged hepatitis, chronic hepatitis, the carrier state and certain other post-hepatitis states of uncertain relationship. Some of the problems in diagnosis and changing concepts in treatment are presented. An attempt is made to evaluate the present status of the multiple problems associated with the prevention and control of viral hepatitis, particularly in respect

to those infections acquired from blood and its derivatives.

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Case Reports

Vitamin A Poisoning in Adults*

With Description of a Case

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THE present report concerns an adult with long standing vitamin A poisoning who had the highest fasting blood vitamin A level ever recorded. During the course of her intoxication, which lasted eight and one-half years, she was hospitalized ten times. Before the correct diagnosis of hypervitaminosis A was established the following diagnoses had been considered: brain tumor, serous meningitis for which she underwent a subtemporal decompression, chronic encephalitis, viral radiculoencephalitis, psychoneurosis and generalized infectious arthritis. For the first time x-ray evidence of bone involvement in an adult is described.

HISTORICAL

As early as 1857 acute illness had been described by arctic explorers following the ingestion of polar bear liver. Elisha Kane mentioned "vertigo, diarrhea, and their concomitants" as the aftermath of eating this food.[1] Jackson[2] in 1899 mentioned that many arctic explorers of that period knew of the poisonous qualities of polar bear liver. It was not until 1942, however, that the toxic substance in polar bear liver was identified by Rodahl and Moore[3] as being vitamin A.

The first reports of toxic effects of excess vitamin A in animals appeared in the late 1920's and early 1930's. von Drigalski administered a vitamin concentrate rich in vitamin A to white rats.[4] In four to six days these animals showed dishevelled fur and marked emaciation. After five to eight days conjunctivitis, hemorrhagic rhinitis and diarrhea appeared. Within five to nineteen days the animals died. Collazo and Rodriguez conducted similar experiments.[5] They noted inflammatory changes of the eyes, bilateral exophthalmos, cessation of growth and spontaneous fracture of bones in addition to trophic changes of the skin and loss of hair. When the overdosage was stopped, the animals recovered and gained weight. Russo was unable to duplicate these effects in animals and concluded that high doses of vitamin A were not toxic.[6] Clausen in an excellent review of the experimental work on this subject came to the conclusion that "the literature was so contradictory at that time (1938) so as to afford no evidence that vitamin A would have a harmful effect on human beings."[7] Subsequently, Moore and Wang[8] produced fatal uterine hemorrhage in adult pregnant rats by the administration of toxic doses of vitamin A.

In 1912 Czerny administered large doses of cod liver oil to tuberculous children and observed the development of seborrheic dermatitis of the face and scalp.[9] Getz and his associates administered 50 cc. of halibut liver oil (2,000,000 units of vitamin A) in a single dose to four adults.[10] All experienced dull headaches but no other symptoms. Rodahl and Moore cite the instance of a man who consumed 6,000,000 units of vitamin A daily for five days at which time he became severely ill, complaining mainly of dizziness. On stopping the vitamin A he rapidly recovered and appeared to be normal within ten days. Clinical recognition of chronic vitamin A poisoning was first described in a child by Josephs in 1944.[11] Since then other reports have appeared, mainly in pediatric literature. By 1952 Caffey had listed twenty-two reported cases in children.[12] Only two cases of chronic hypervitaminosis A have been reported in adults, neither of whom exhibited the advanced changes present in our patient.[13,14]

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CLINICAL CLASSIFICATION

A clinical classification suggested by Knudson and Rothman divides hypervitaminosis A into acute and chronic forms as they exist in infants and adults.[15]

Acute Hypervitaminosis A in Infants. Acute hypervitaminosis A in infants resulting from accidental ingestion of large doses of vitamin A has been reported by Marie and See, by Mulloy and by Garcia.[16–18] In addition to vomiting and drowsiness, there was marked bulging of the fontanelle in every case. During their illness there were no evidences of cervical rigidity, abnormal neurologic signs or fever. In every instance recovery was rapid and complete following lumbar puncture and abstinence from vitamin A. In Mulloy's case the anterior fontanelle bulged 2 cm. The spinal fluid was under greatly increased pressure and contained 30 cells of which 98 per cent were lymphocytes. The Pandy test was slightly positive and no bacterial growth was obtained. The serum vitamin A level on admission was 715 units, and after four days without vitamins fell to 217 units.* A fine cutaneous desquamation developed over the trunk and extremities after a few days.

Acute Hypervitaminosis A in Adults. Symptoms of acute hypervitaminosis A in adults appear within four to eight hours following ingestion of toxic doses of vitamin A. Headache is the predominant manifestation and has been described as being violent and localized in the forehead and eyes. Nausea, vomiting, vertigo, drowsiness, irritability and localized or generalized peeling of the skin are common findings. Lonie reported a family with vitamin A poisoning following a meal of shark liver.[19] Their symptoms consisted of severe headache, dizziness, nausea and vomiting. Recovery was rapid and complete. Within thirty-six hours desquamation of the skin started and later became extensive.

Chronic Hypervitaminosis A in Infants. In 1944 Josephs reported the first case of chronic hypervitaminosis A in a child.[11] Toomey and Morissette in 1947 described a similar case.[20] They were able to reproduce the original symptoms and signs in this two year old infant by giving 6,200,000 units of vitamin A during a period of fourteen days. Gribetz, Silverman and Sobel[21] reviewed the literature and summarized the findings in seventeen cases, including two cases of their own. Most instances occurred in the second or third year of life and followed months of excessive vitamin A intake. The most prominent features were cortical thickening of the bones, painful swellings in the extremities, irritability, pruritus, hepatomegaly, limitation of motion or inability to stand, sparse coarse hair, fissuring of the lips, constipation and a failure to gain weight. Splenomegaly was noted only by Josephs.

Gribetz et al. reported the case of a seventeen month infant who had enlargement of the head. Slightly dilated ventricles on pneumoencephalogram and ventriculogram suggested hydrocephalus. Following a reduction in vitamin A intake her head assumed normal proportions. A six and one-half month old girl with chronic hypervitaminosis A was described by Arena as having marked craniotabes.[22] X-ray of the skull showed uniformly thin bones. There was no hyperostosis. After elimination of all vitamin preparations the skull bones became normal.

Chronic Hypervitaminosis A in Adults. Only two cases of chronic hypervitaminosis A have been reported in adults. Sulzberger and Lazar in 1951 described a forty-four year old woman who, in an attempt to prevent "colds," had taken 600,000 units of vitamin A daily for eighteen months, supplemented by occasional doses of 1 to 2 million units.[13] Her complaints and findings included the following: menstrual periods of shorter duration and decreased flow; generalized joint and bone pains; soreness and fissuring at the corners of the mouth and nasal apertures; dry rough skin with brawny desquamation, peculiar pigmentation, excessive loss of hair, and generalized pruritus; night sweats; and increased prominence of the eyes. Note should be made that x-rays of several long bones and joints revealed normal features, and that headaches were not included as part of the symptomatology. Her highest vitamin A level was 60 blue units.*

Bifulco[14] in 1953 presented the case of a fifty-two year old woman with a four-year history of daily intake of 100,000 units of vitamin A. After one year on this regimen insomnia and listlessness appeared. Subsequently, loss of hair, stiffness and pain in the joints, a patch of pigmentation on the forehead, and increased prominence of the eyes were noted. Because of possible dental infection, teeth were extracted with resultant severe hemorrhage. Anorexia, marked loss of weight and spontaneous oozing of blood from the nose appeared. Menses, which had become irregular about one year after the onset of vitamin

* 1 μg. of vitamin A = 3.33 U. S. P. units.

* Normal = 10 to 20 blue units.

A ingestion, ceased within the following two years. The eyes were prominent and pulsated, and the fundi disclosed abnormal pulsation of the retinal veins. A thumping headache developed one month prior to the cessation of vitamin A ingestion and was still present six months after all vitamin A had been stopped. Cerebral angiography was performed but failed to disclose an aneurysm. There was pain on flexion of all joints and marked tenderness was elicited over the long bones of the extremities. There was no joint swelling or deformity. No mention was made of x-rays. Headache and pulsation of the right eye persisted at the time of the report, all other manifestations having returned to normal several weeks after vitamin A was stopped.

CASE REPORT

S. L., a twenty-one year old unmarried white female was admitted on July 24, 1945, to hospital "A." Her chief complaints were diplopia for five weeks and headaches and nausea for four weeks. Five weeks prior to admission she noted blurring of vision followed by diplopia. This persisted and was in turn followed by severe frontal headaches and nausea. Three weeks prior to admission the patient began to have incontinence of urine and nocturia, as well as occasional enuresis. She also developed urgency and frequency but no burning on urination. Systemic review revealed occasional joint pains occurring with inclement weather. She had a cold for two weeks, and a cough for one week prior to admission. Her family history revealed hypertension in two grandparents and cancer in a third. Menses began at twelve years with regular thirty-day cycles lasting five days with a normal flow. There was occasional dysmenorrhea. She smoked one pack of cigarettes a day.

The physical examination at this time showed temperature 99.6°F., pulse 84, respirations 20, blood pressure 105/75. She was a well developed, well nourished white female in no distress. The eyes reacted equally to accommodation and light. Pupils were round, the left slightly larger than the right. There was internal strabismus with uncrossed diplopia and nystagmoid twitchings in both lateral gazes, right more than left. After repeated lateral eye movements the nystagmus became more sustained. Fundus examination showed both discs hyperemic, margins slightly blurred, slight venous congestion and a tiny hemorrhage near the right disc nasally. Bone conduction was greater than air conduction on the left. Facial sensations, corneal reflexes and jaw motion were normal. Hearing was normal. Tongue movements, swallowing and taste were normal. The neck was supple and no glands were palpable. The lungs were clear to percussion and auscultation. Examination of the heart showed regular sinus rhythm, P_2 greater than A_2, the point of maximal impulse in the fifth intercostal space. There were no thrills or murmurs. The liver, spleen and kidneys were not felt and no abdominal tenderness was present. No costovertebral angle tenderness or vertebral tenderness was elicited. Motor power was normal in all limbs. The reflexes were symmetrical and equal throughout except for the right knee jerk which was greater than the left. No pathologic reflexes were elicited. The finger to nose, heel to knee and pronation-supination tests were normal. Light touch and pinprick were normal throughout. Position and vibration were appreciated in the great toes; however, vibration was diminished generally on the left. Gait and speech were unimpaired. The patient was alert, intelligent and cooperative.

X-ray of the skull showed some increase in the digital markings of the cranial vault. The sella turcica was normal in size and shape. No abnormal calcifications were demonstrated. Examination of the skull following direct ventricular injection of air showed that the anterior horns were well outlined. They showed some dilatation but no evidence of a shift. The bodies of both lateral ventricles, however, were poorly outlined. The posterior and inferior horns appeared normal. The visual fields on two separate occasions showed a small but definite constriction bilaterally, the left slightly more than the right. Visual acuity was O.D. 10/15, O.S. 10/10.

The laboratory findings were as follows: urinalysis, 1 plus albumin on 2 occasions; red blood count 4,000,000; hemoglobin 81 per cent; white blood count 10,700, with a normal differential count; E.S.R. 3 mm./one hour; spinal fluid, glucose 56 mg. per cent, total protein 31 mg. per cent; ventricular fluid from the right side, total protein 15.6 mg. per cent; serologic tests for syphilis negative in blood and spinal fluid.

During the patient's stay a definite increase in the degree of choked disc was noted, more papilledema being present on the right than on the left. When she looked to the right the nystagmus was definite and well sustained, the right

lateral deviation being greater than on the left. The patient also began to notice diplopia on straight gaze. On occasion she complained of pain in her left trapezius region and left leg. Ventriculography was done, both anterior ventricles being tapped. A moderate amount of clear colorless fluid escaped under increased pressure from the right anterior horn. When the head was tilted no additional fluid was obtained from the right anterior horn and therefore the left anterior horn was entered. Although air had been injected into the right anterior horn under increased pressure, no air bubbles appeared in the brain cannula when the left anterior horn was tapped and the fluid which escaped seemed to be slightly cloudy. Ventriculograms revealed the lateral ventricles to be normal in shape, size and position. The third and fourth ventricles were not well visualized. An electrocephalogram suggested posterior fossa tumor or some other subtentorial disturbance.

The patient left the hospital on September 6, 1945, with a diagnosis of intracranial neoplasm. Six days later she was admitted to hospital "B." At this institution additional history was obtained. The patient stated that she had "icthyosis" as long as she could remember and had been taking large doses of vitamin A for the past one and one-half years with remarkable improvement of the skin. Otherwise both history and physical examination were unchanged. X-ray of the skull confirmed the impression of increased intracranial pressure. Because of the normal lateral ventricles the neurosurgeon believed that poor visualization of the third and fourth ventricles was not due to obstruction at the foramen of Monro, aqueduct of Sylvius or the fourth ventricle. He favored a diagnosis of serous meningitis and performed a right subtemporal decompression. There was a continued outpouring of fluid after the dura was incised.

She was readmitted to hospital "B" on August 15, 1946, approximately eleven months after her previous discharge. She had remained "relatively well" until six weeks before this admission, when she began to have pain in the region of the seventh right rib in the anterior axillary line. This pain seemed to spread posteriorly to the region of the ninth thoracic vertebra and later also to the right ninth costochondral junction. At times she noticed that her legs began to feel heavy. Three days before admission she noticed numbness in the saddle area. Her right-sided chest pain was accentuated by coughing and sneezing but not by straining. It was also increased if the patient lay on her abdomen.

Physical examination at this time revealed a markedly bulging area at the site of the previous subtemporal decompression. The neck was quite supple but extreme flexion caused the patient's chest pain to appear. Although the fundi showed rather full veins, the discs were well outlined. There was some diplopia on left lateral gaze and some left central facial weakness. Sensory and motor findings were normal. Reflexes were active and equal except for some hyperactivity of the biceps jerk on the left. Hoffmann's sign was positive bilaterally. There was localized tenderness over the lower chest wall at about the ninth right rib anteriorly. No spine tenderness was elicited.

Studies at this time showed the urine and the blood count to be normal. The urea clearance test and the blood sugar, urea nitrogen, total protein and cholesterol were within normal limits. The cephalin flocculation and thymol turbidity tests were normal. A lumbar puncture revealed clear fluid under normal pressure with a negative Pandy test. X-ray of the chest failed to reveal any local pathologic condition of the bone. The x-ray of the spine showed some hypertrophic lipping of the contiguous surfaces of the fifth and sixth thoracic vertebrae. Skull x-rays were normal except for the bony defect of the previous decompression. A pneumonecephalogram was likewise normal. Intravenous pyelography showed no abnormality.

During her hospitalization of two and one-half months there was no improvement. She was treated with thiamin chloride for possible intercostal neuritis. Radiation therapy also failed to cause any lessening of her pain. The medical consultant believed that her pain was probably unrelated to her cerebral lesion. The neurologist suggested that such pain is often the result of medulloblastoma metastases, although in this case a large psychic element had to be considered. There was no improvement and the patient was discharged with the diagnosis of costalgia, cause unknown.

The patient was admitted to hospital "C" on February 10, 1947, because of persistence of her complaints. Examination revealed a markedly bulging right subtemporal decompression. The fundi showed pallor and the disc margins were somewhat indistinct. There appeared to be atrophy of the right rhomboid and supra-

scapular muscles. The right scapula was winged. The patient stood in a position of forward flexion and because of pain in the right hip and knee favored the right lower extremity in walking. Blood studies included a serum phosphorus of 4.0 mg. and alkaline phosphatase of 6.2 units.

X-rays of the chest, dorsal spine and foramen magnum were considered normal. Fever therapy with typhoid vaccine was given but the results, while definite, were far from dramatic. A tantalum cranioplasty was performed and the patient was discharged on April 7, 1947. The discharge diagnosis was chronic encephalitis.

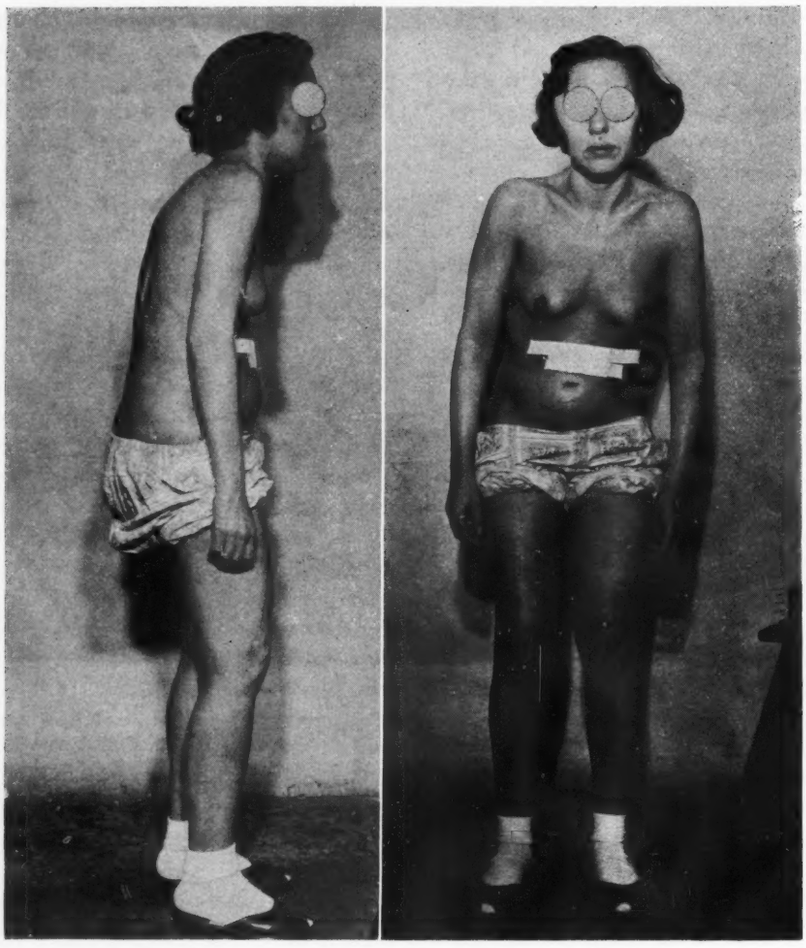
One month later the patient was admitted to hospital "D" with a febrile illness of eight days' duration during which period the pains in her knees, elbows, right hip and left shoulder had become aggravated. The exact nature of this acute illness was never determined. While physical examination of the chest was always negative, indefinite findings on lung x-ray suggested a pneumonitis. Many tests and observations were made during this hospitalization, the most significant of which were: sparse eyebrows, pigmentation over the skin of the abdomen, hepatosplenomegaly, moderate anemia and marked tilting of the pelvis. Tests for liver function were normal, including BSP and hippuric acid excretion tests.

During this hospitalization her bone and joint pains continued and her deformity seemed more marked. It was noted that while the pain in her back persisted, she was comfortable when perfectly quiet. Her greatest difficulty occurred with change in position after a period of rest. The back muscles showed spasm of moderate degree and there was a flexion contracture of the right hip. The hip joint was entirely normal, motion in all directions being free and painless, with no tenderness present. Moderate tenderness was noted in the right iliolumbar angle, with negligible tenderness of the spine and sacroiliac joints. A plaster of Paris spica was applied from the nipple line to the middle of the right leg. On July 14, 1947, she was discharged. When she returned five weeks later for removal of the cast there was no apparent improvement. At this time the liver was felt one and one-half fingerbreadths below the costal margin. The skin was uniformly hyperpigmented, dry and shiny. The palms were cracked and scaling. One neurologist believed that the picture was one of cerebral and posterior root disorder, at various times affecting the thoracic and lumbosacral segments. He believed that the hepatosplenomegaly had a common etiology with that of the neuropathology and therefore diagnosed encephaloradiculitis due to a virus infection.

The patient re-entered hospital "D" for the third time in five months because physiotherapy, which had been started during her previous admission and continued while at home, failed to arrest the progress of her disease or alleviate her symptoms. It was noted that she had continued to take 500,000 units of vitamin A daily for her skin condition and this was continuously administered during her hospital stay. Right lateral rotatory nystagmus was present. The lips showed desquamation, and the pigmented skin was noted to be most prominent over the left mid-abdomen. Tests for Addison's disease were negative. Biopsy of the skin did not show hemosiderin deposits. The basal metabolic rate was minus 1 per cent. Special oblique studies of the lumbar vertebrae showed no abnormality, although she now had a completely rigid "poker" spine. A plaster jacket was applied from the groin to the axilla with considerable relief. At the time of discharge on November 11, 1947, she still had a two-fingerbreadth enlargement of the liver.

Five months later, April 6, 1948, she had a muscle biopsy at hospital "E." Microscopic sections failed to reveal lymphoid infiltration. The following month she was readmitted because of multiple severe joint pains and inability to walk straight. The physical examination showed diplopia on lateral gaze, limited chest expansion, drooping right shoulder, elevated right hip, shuffling gait, bilateral hip limp, rigid back, generally limited joint motion, trunk inclined forward and flexion contractures of the knees and hips. X-ray studies were read as showing incomplete fusion of the bodies of the fourth and fifth cervical vertebrae, an ankylosing process of the upper dorsal spine, a slight list of the lumbar spine to the left without evidence of an arthritic process, and moderate arthritic changes in both sacroiliac joints.

The following were described as radiographically normal: chest, right shoulder girdle, both hips and right knee. Laboratory studies revealed an elevated sedimentation rate and increased blood alkaline phosphatase. The patient was treated with orthopedic measures and discharged to the outpatient department for continued physiotherapy. The discharge diagnoses were



1A 1B

FIG. 1. A and B, patient at time of admission. Note bulge in right temporal area.

Marie-Strümpell arthritis and generalized infectious arthritis.

During the next five-year period she was treated by chiropractic and osteopathic methods with no improvement in her status. Bone pains had increased and disability was more marked. She continued the use of vitamin A in doses of 500,000 units daily.

She first came under our care on February 5, 1953. We were aware of reports dealing with the toxic effects of vitamin A and suspected that our patient's illness could be on this basis. Accordingly, blood was drawn and examined for vitamin A content. When this was found to be unusually high, hospitalization was advised.

She was admitted to the Jewish Hospital of Brooklyn on February 12, 1953, because of progression of the complaints for which she had been previously hospitalized. In the past five years she had lost 20 pounds as a result of anorexia, severe diffuse pruritus and inability to sleep because of pain.

Examination revealed an alert, cooperative, intelligent female in constant pain aggravated by any attempt to change her position. (Figs. 1A and B.) The blood pressure was 110/70, pulse 90 and respirations 18 per minute. The right subtemporal decompression was tense and bulged markedly. Her pupils were round, regular, equal in size, and reacted to light and accommodation. Neither diplopia nor nystagmus was present. The fundi were normal. The mucous membranes of the mouth were normal. Many teeth were missing but those remaining were normal. No adenopathy was present. The thyroid gland was not palpable. The breasts were normal. The lungs were clear to percussion and auscultation and the heart was normal. No abdominal masses or organs were palpable. Rectal examination was negative. The results of

neurologic examination were as follows: cranial nerves intact; cerebellar tests normal; sensory and motor systems intact; reflexes equal throughout except for the right knee jerk which was greater than the left; no pathologic reflexes. Dermatologic findings were: thinning of scalp hair, axillary hair and eyebrows; nails normal; skin diffusely pigmented, coarse over most of the body, but dry, shiny and somewhat atrophic with associated loss of lanugo hair over the arms and legs; elbows keratotic and scaly; palms and soles scaling, with deeply marked furrows and dried blebs; many scratch marks throughout. Orthopedic examination showed: temporomandibular joints and facial muscles normal; neck movements normal in range and strength; spine fixed in extension although tilted forward and slightly to the left, without tenderness but painful on motion; extreme paravertebral wasting; rib cage fixed and tender on compression; right shoulder painful on elevation to 90 degrees and fixed after 110 degrees; elbows, wrists and fingers normal; left hip relatively normal; right hip painful with limitation of terminal 30 degrees of extension and 50 degrees of abduction; the feet showed fixed hallus valgus.

Laboratory studies were as follows: hemoglobin 74 to 81 per cent (15 gm. = 100 per cent); red blood count 3.7 to 4.4 million; white blood count 6,400 to 7,400; polymorphonuclears 64 per cent, bands 1 per cent, lymphocytes 31 per cent, monocytes 2 per cent, eosinophils 1 per cent, basophils 1 per cent, platelets adequate; hematocrit 42 per cent. Bone marrow aspiration normal; myeloblasts 5 per cent, neutrophilic myelocytes 9 per cent, eosinophilic myelocytes 0, metamelocytes 38 per cent, staff forms 39 per cent, polymorphonuclears 6 per cent, eosinophils 3 per cent, megakaryocytes adequate, granulocyte:polymorph ratio 91:9; granulocyte:erythrocyte ratio 90:10; red cell sedimentation rate 22 mm./one hour; bleeding time two minutes; clotting time three minutes fifteen seconds; urinalysis, specific gravity 1.022, albumin 0, sugar 0, microscopic examination negative; basal metabolism, plus 12 and plus 10; electrocardiogram within normal limits. (See Table 1 for chemical determinations.)

The results of x-ray examination were as follows: Skull: right subtemporal decompression with tantalum plate *in situ;* slight thinning of vault of skull; slight hyperostosis frontalis interna. Shoulders: thinning of wings of scapulae, more marked on left; thin rim of calcification parallel to rim of glenoid fossa. Ribs: normal. Dorsal spine: narrowed intervertebral spaces with thinly calcified anterior spinal ligament; moderate decalcification of vertebral bodies; pedicles and laminae intact; interpedicular distances normal. Lumbar spine: straightened lordotic curve; moderate decalcification of vertebral bodies; intervertebral spaces normal; minimal spur formation at anterior aspects of

TABLE 1
BLOOD DETERMINATIONS

	February 13	March 3	April 14
Sugar*	100	96	73
Uric acid*	4.2	3.7	4.0
Urea*	15	15	16
Icterus index	9.6	12.0	11.5
Ca*	9.4	9.3	8.9
Total protein, gm./100 cc.	7.5	.....	7.6
Albumin/globulin ratio	1.6	.....	1.6
Vitamin C* (normal = .7–2.5)	0.7	.....	.....
Bilirubin, free*	0.3	.....	.....
Bilirubin, total*	0.7	.....	.....
Total cholesterol*	207	227	222
% Free cholesterol	32	28	28
CO_2 combining power (vol. %)	61.6	60.9	56.0
Sodium*	331	322	318
Potassium*	16.3	18.1	13.9
Chloride*	328	342	352
Inorganic phosphorus*	3.8	3.4	4.1
Alkaline phosphatase†	3.3	3.6	3.7
Cephalin flocculation	0	.....	.....
Thymol turbidity	4.4	.....	.....
Amylase (somogyi units)	70	.....	.....
Amylase control	72	.....	.....
Amino acid*	7.4	.....	.....
Total fatty acids*	330	.....	.....
Phospholipid phosphorus*	10.5	10.4	.....
Total lipid (Bloor method)*	418	.....	.....
Prothrombin time	14.4 sec.	14.0 sec.	.....
Prothrombin time control	10.1 sec.	11.2 sec.	.....
Protein-bound iodine μg./% (normal = 3–8)	.....	.....	1.8

Citric Acid* (normal = 1.5–2.6)

Date	
2/23	1.9
2/24	1.9
2/25	1.8
2/26	1.7
2/27	1.7

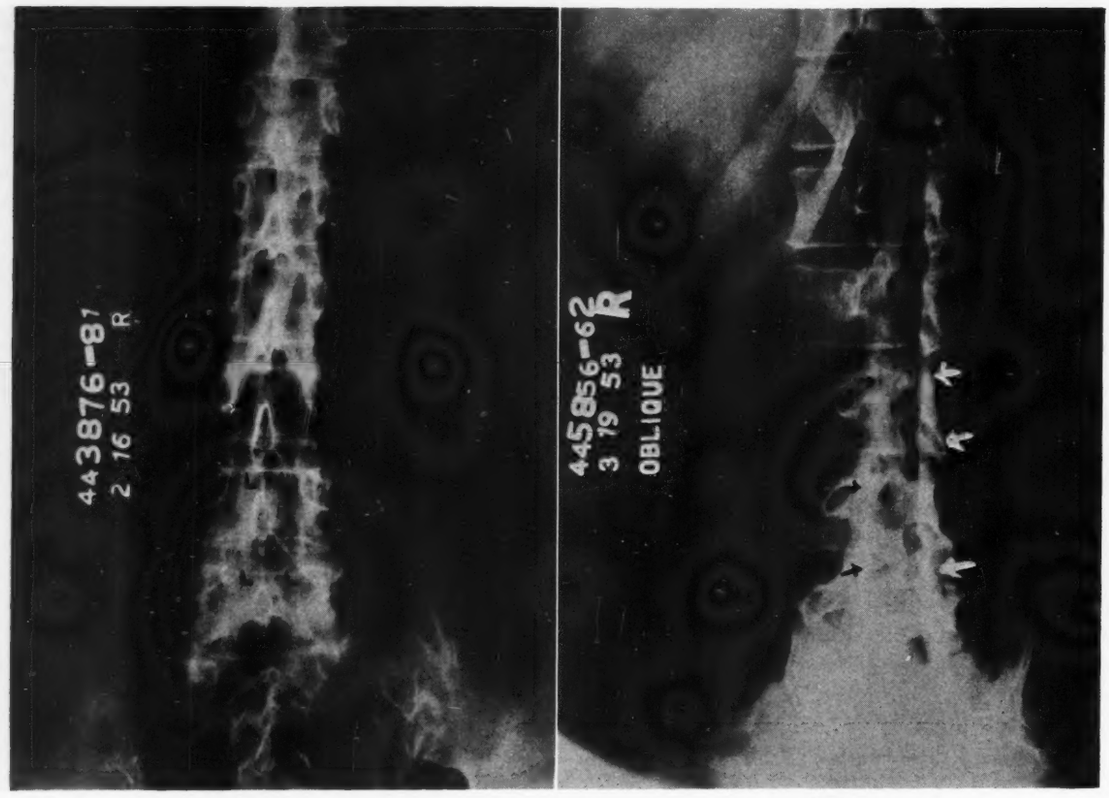
Prothrombin consumption test: 48.6 sec.
Prothrombin consumption control: 43.4 sec.
Prothrombin Dilution Test:

100% Plasma	13.2 sec.
75% Plasma	16.8 sec.
50% Plasma	21.8 sec.
33% Plasma	30.5 sec.
16.5% Plasma	59.3 sec.

* Milligrams per 100 ml.
† Bodansky units.

URINE DETERMINATIONS
(*Twenty-four-hour Excretion*)

Calcium	726 mg./1,260 ml.	(Normal = 100–300 mg.)
Citric acid	760 mg./total 914.5 mg./1,180 ml.	(Normal = 200–1,200 mg.)
Phosphorus	878 mg./1,260 ml. 652 mg./1,180 ml.	(Normal = 800–1,300 mg.)



2A 2B

FIG. 2. A, anteroposterior roentgenogram of lumbar spine. Note the calcification in the ligamenta flava (letters L overlying these structures between the third and fourth and fourth and fifth lumbar vertebrae). Similar changes exist in the ligamenta flava between the neural arches of the upper lumbar vertebrae. B, right posterior oblique roentgenogram of lumbar spine. The white arrows point to the calcified ligamenta flava. The black arrows indicate the loss of definition of the apophyseal joints, with narrowing of the joint spaces.

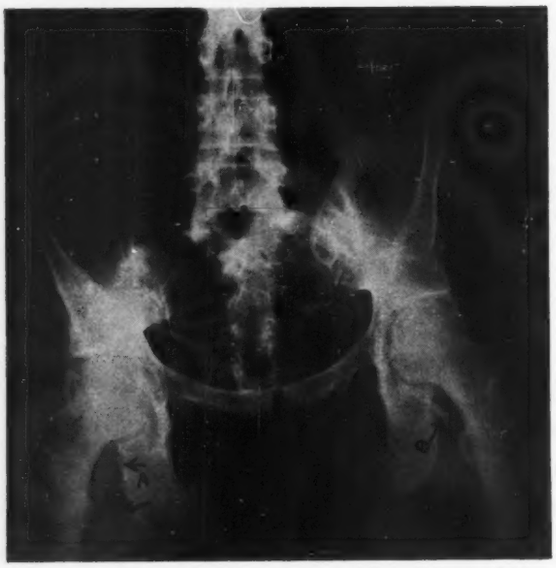


FIG. 3. Anteroposterior roentgenogram of pelvis. Periosteal elevation along ischial ramus (A), and calcification in articular capsule (B) are indicated by the respective black arrows.

upper lumbar vertebral bodies; apophyseal joints narrowed, with loss of definition of their articular surfaces; moderate calcification of ligamentum flavum; slight calcification of iliolumbar ligaments. (Figs. 2A and B.) Pelvis: sacroiliac joints normal; pelvic inlet distorted because of inability of patient to assume recumbent position; calcification in periosteal elevations and probable bone formation in lateral aspects of both iliac bones just above acetabular sockets; calcification in capsule of hip joint at insertion into superior rim of acetabulum bilaterally; similar but lesser degree of calcification in inferior aspects; shaggy appearance of ascending ramus of right ischium; a single spur-like projection of ascending ramus of left ischium and of lesser trochanter of right femur. (Fig. 3.) Hands: normal. Feet: normal. Knees: calcification at anterior tibial tubercles and anterior inferior aspects of patellas bilaterally; local thickening at upper medial aspect of left tibia; bony densities not disturbed. (Fig. 4.) Os calcis: calcification at

insertion of achilles and plantar tendons bilaterally.

Skin biopsy from the mid-abdomen showed moderate hyperkeratosis with thickening of the granular layer which contained foci of dyskeratosis as evidenced by marked vacuolization of the cells; dense hyperpigmentation of the basal layer with intracellular melanin involving some of the overlying cells of the prickle layer; normal corium. The diagnosis was hyperkeratosis with pigmentation.

Bone biopsy from the right tibial tubercle showed broad osseous trabeculae which in places presented calcification of the cartilage, thickening of the periosteum and normal marrow spaces. (Fig. 5A and B.) The diagnosis was calcification in cartilaginous tissues with thickened periosteum.

Immediately after the patient was admitted to the hospital all vitamin A medication was stopped and she was given a normal hospital diet.* Within two and a half weeks her itching had disappeared and there were no further evidences of scratch marks. At the end of one month her skin texture had improved, her bone pains were markedly diminished, her appetite was excellent and she had gained weight. Six weeks after admission she woke one morning with marked dizziness and diplopia. There was no headache. Nystagmus was present on lateral gaze. The fundi were normal. Her diplopia gradually receded and was completely gone by the end of one week. Two months after vitamin A medication had been stopped, all spontaneous pain had gone and no further sedation was needed. Her posture had begun to improve.

During her stay she had three normal menstrual periods occurring at monthly intervals and lasting five days with a normal flow. Her improvement was continuous and she was discharged on April 26, 1953.

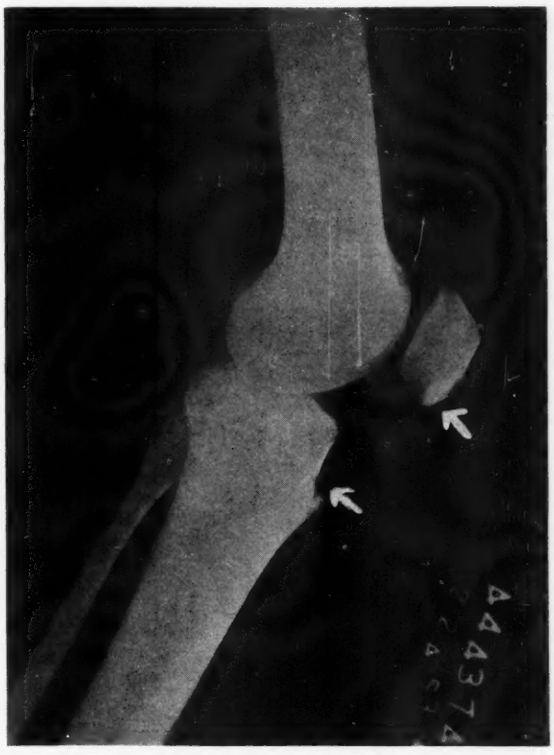


FIG. 4. Lateral roentgenogram of left knee. White arrows point to calcification in infrapatellar ligament.

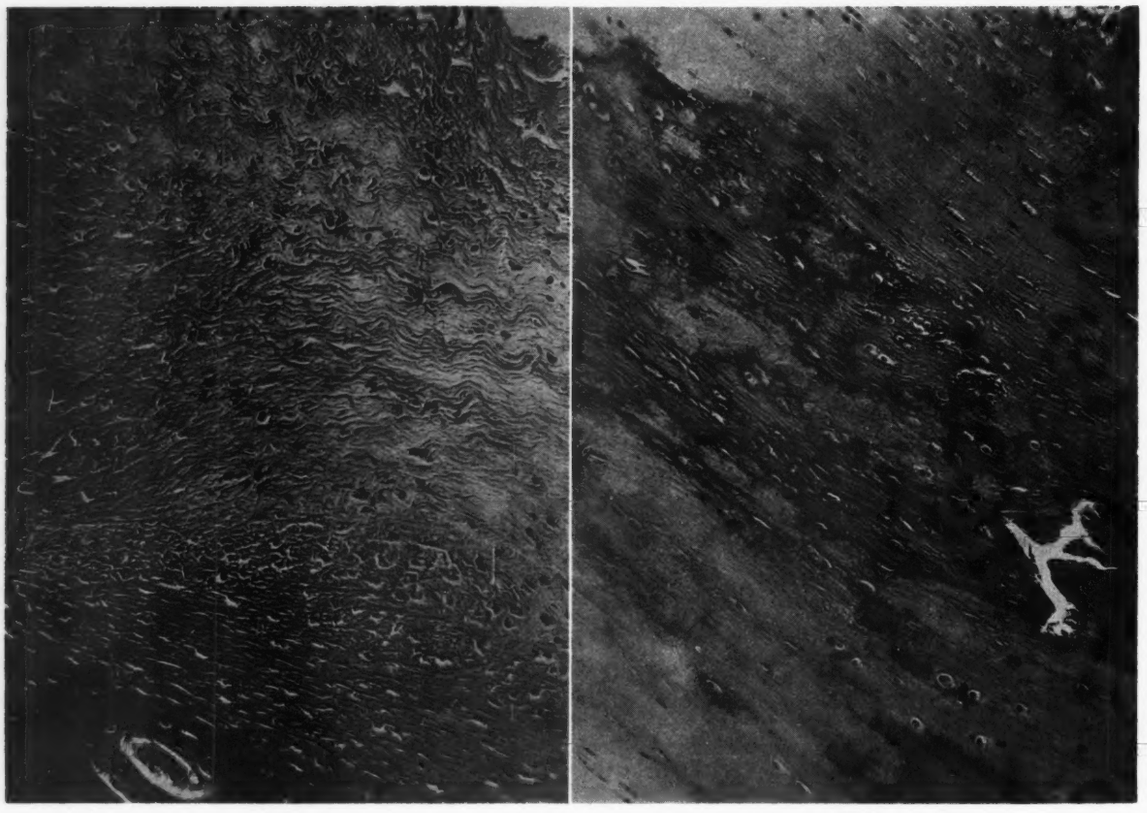
COMMENT

Hypervitaminosis A may result from the ingestion of large amounts of vitamin A concentrates taken alone or in combination with other vitamins or minerals. Large doses of vitamin A are used in the treatment of skin, eye, renal, gynecologic and ear disorders as well as the common cold. The minimal daily requirement of vitamin A is 5,000 to 7,000 international units. In the usual diet this requirement is derived from both vitamin A and its precursor carotene, which is converted in the intestinal wall and possibly elsewhere, into vitamin A.[23–35] The conversion of carotene to vitamin A is limited and may not provide sufficient vitamin A to maintain the patient during stress.[36] Moreover, there is evidence to indicate that the conversion of carotene to vitamin A is impaired in some diseases, such as diabetes.[37–44]

Vitamin A is absorbed as the free alcohol and is esterified in the intestinal wall. Following vitamin A intake the rise in serum levels is due to the ester fraction, most of which is then deposited in the liver as such.[21,45] Vitamin A alcohol levels are not directly influenced by ingestion. The vitamin A alcohol level seems to be a measure of vitamin A storage.[46] In severe infection, in hepatocellular disease and in vitamin A depletion the plasma vitamin A alcohol level is usually low. The normal vitamin A blood level is 30 to 70 μg. and may rise to 1,000 to 2,000 μg. soon after the ingestion of very large doses of vitamin A. This is a temporary state and does not alter the subsequent fasting level.

The fasting level of 2,000 μg. per 100 cc. in our patient is the highest reported in man. Unlike such high levels observed following administra-

* 7,500 units of vitamin A daily.



5A 5B

FIG. 5. Right tibial tubercle biopsy. A, note the marked periosteal thickening; B, note the calcification in the cartilaginous tissue.

tions of vitamin A, most of the blood vitamin A content in this patient was in the form of the free alcohol, not as ester. This high percentage of vitamin A alcohol with high total blood levels of vitamin A has been observed in a child reported by one of us.[21] There is a possibility that not only the total vitamin A but the relatively high percentage of alcohol has significance in the diagnosis of hypervitaminosis A. In the previously reported adult cases the vitamin A level was 60 blue units* in one and unrecorded in the other.

The high vitamin A blood level of our patient was the result of continued daily ingestion of vitamin A for eight and one-half years. After four months of taking 25,000 units daily, she increased her dosage to 50,000 units and then rapidly to 500,000 units daily. On occasion, an additional dosage of 500,000 units was taken. The preparations of vitamin A which she had taken were stated by their manufacturers to be free of vitamin D.

During the course of this study, we had the opportunity of examining the blood of four other patients who had taken large doses of vitamin A over prolonged periods of time. While we cannot be certain that blood levels are a good index of vitamin A storage, they may be an index of toxicity since the transfer of vitamin A in the body is related to blood levels rather than to the total amounts of vitamin A stored. One patient had taken 25,000 units daily for three years, then 25,000 to 50,000 units for the next three years, and finally 50,000 to 100,000 for two years. Her fasting blood level was 120 μg. per 100 cc. Another patient who consumed between 25,000 and 50,000 units daily for six years had a fasting level of 88 μg. per 100 cc. A third patient took 25,000 units daily for six years and had a normal fasting level of 60 μg. per 100 cc. A fourth patient who took 50,000 units daily had a fasting level of 225 μg. per 100 cc. after eight months. Only the first and last patients had any complaints referable to possible vitamin A toxicity. Both had headaches which subsided soon after they stopped vitamin A therapy. It is apparent that individual factors

* Normal = 10 to 20 blue units.

greatly affect the size and duration of the dose that will produce toxic effects.

Daily vitamin A plasma levels were determined during the eleven weeks of hospitalization to observe changes in the blood levels while the patient was on a normal hospital diet. (Fig. 6.)

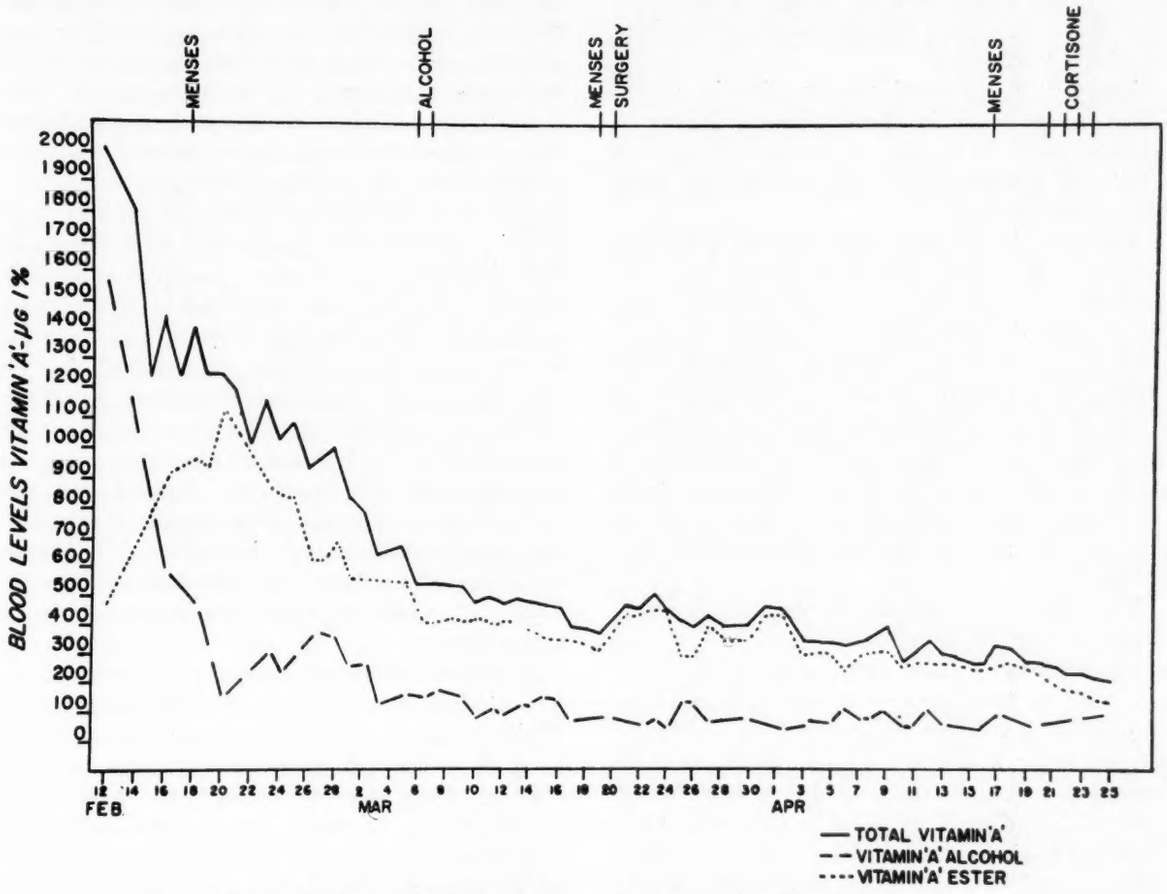


FIG. 6. Vitamin A blood levels during first ten weeks of hospitalization.

Vitamin A partitions into the alcohol and ester, together with the carotene level, were followed daily. Apart from the admission blood carotene level of 360 µg. per 100 cc., all carotene levels were between 180 and 290 µg. per 100 cc. (normal 54 to 310). At the onset the vitamin A levels, while extremely high, maintained the ratio of 20 per cent ester to 80 per cent alcohol. Immediately after stopping the vitamin A intake, there was a precipitous fall in the total vitamin A level, which reflected a parallel fall in the vitamin A alcohol. (Fig. 6.) However, during the first week while the alcohol fraction was falling, the ester fraction showed a very marked rise so that the ratio of ester to alcohol became reversed. This reversed ratio persisted.

We cannot establish from this study whether the alcohol, ester or total vitamin A level in the blood is the best measure of vitamin A storage, as we did not attempt to assay the liver or other tissues for vitamin A content. We are unable to explain the change in serum vitamin A alcohol-ester relationship in the light of present concepts of vitamin A metabolism. Is the vitamin A now being transported from the liver to the tissue in the form of ester? Has excess vitamin A in ester form been deposited in depots other than the liver, and is it now being released to the circulation in this esterified form? This would be consistent with the disappearance of hepatic enlargement. While the patient presented hepatomegaly during a six-month period, it was not present during the latter years of her illness in spite of continued excessive intake of vitamin A. This would not be expected if liver enlargement is considered an expression of vitamin A deposition. Repeated laboratory studies during her illness showed no evidence of impaired liver function, even when hepatomegaly was present. While liver enlargement has been found

frequently in children with vitamin A toxicity, it has not been noted in the previously reported adults. Splenomegaly, which was present in Josephs' case, was found in our case at one time.

Vitamin A tolerance tests carried out with half and full doses revealed no deviation from the normal. They showed the rise to be in the ester form while the alcohol fraction remained relatively unchanged.

Josephs[11,47] observed that a rise in serum lipids occurs early in the course of vitamin A toxicity, only to return to normal in spite of continued massive dosage. In our case the blood lipids were normal.

Alkaline phosphatase studies made while the patient was under our observation were repeatedly normal. However, six years before, elevated levels were found for a period of more than one year in two different hospitals. This finding is in agreement with the elevated levels found in many of the cases reported in children. This increase in serum alkaline phosphatase is probably associated with an increase in bone metabolism. In a previous adult case no alteration in the serum alkaline phosphatase was noted.

There has been interest in vitamin A as an agent in the prevention of renal calculi. In nephrolithiasis urinary citric acid tends to be low, and it has been observed that aqueous dispersions of vitamin A may cause a rise in the urinary citric acid level with possible resulting increased solubility of calcium stones.[46] We undertook studies of the blood levels and urinary excretion of citric acid, calcium and phosphorus. These blood findings were repeatedly within upper normal limits, as were the urinary excretion of citric acid and phosphorus, both in twenty-four-hour total output and concentration. However, the calcium excretion in the urine was markedly increased in both concentration and amount.

Rodahl[48] found that animals with experimental hypervitaminosis A showed low ascorbic serum levels and decreased amounts of ascorbic acid in the adrenals and liver. Moore and Wang[49] were unable to confirm this finding. Gribetz et al. did not find evidence of vitamin C deficiency in their studies and our patient had a normal vitamin C blood level. There were no clinical manifestations of scurvy.

Studies were made to determine the effects of menstruation, starvation, large amounts of alcohol, cortisone and operative procedures upon the total blood vitamin A levels as well as upon the alcohol and ester fractions.

It has been observed that normal women have a cyclic change in the serum vitamin A level which reaches a minimum at the time of menstruation and a maximum between menstrual periods.[50] This variation was not noted in our patient, who failed to show any appreciable change in relation to the menstrual cycle. The toxic levels exhibited by our patient could well have masked the slight changes noted in normal women with normal blood levels.

On two consecutive days the patient was given a pint of wine in addition to her regular diet. No influence on the vitamin A level was noted. Likewise, no appreciable effect was noticed after short periods of starvation. Because of the report that cortisone causes depletion in the amount of vitamin A present in the liver of the rat, our patient was given cortisone in doses of 300, 200, 100 and 100 mg. consecutively for four days.[51] No significant changes occurred in the vitamin A levels. This does not mean that the vitamin A stores were not affected. It would be of interest to observe the effect of cortisone in a patient presenting acute symptoms of hypervitaminosis A.

Biopsy of the tibial tubercle was performed under intravenous sodium pentothal anesthesia. There was a seventy-two-hour rise in the level of vitamin A from 350 μg. to a peak of 490 μg. This was due entirely to an increase in the ester fraction. During the following seventy-two hours the esters returned to their previous level. The alcohol fraction, which had remained unchanged throughout, rose markedly on the fifth and sixth postoperative days and then fell to the previous level. This vitamin A must have come from the body stores and it is interesting to note that the original rise was in the ester rather than in the alcohol fraction.

NEUROLOGIC CONSIDERATIONS

There is much evidence to indicate that vitamin A poisoning may produce intracranial disturbances.[15,16,18] In infants massive doses of vitamin A resulted in a marked increase in the cerebrospinal fluid pressure with bulging of the fontanelle. Cerebral manifestations such as severe headache, nausea, vomiting, dizziness, drowsiness and irritability are seen in adults

who receive massive doses of vitamin A.[3,10,19] Both Gribetz and Arena have reported enlargement of the head in children with chronic hypervitaminosis A. In each instance there was a return to normal following withdrawal of vitamin A medication. In the case reported by Bifulco headaches played a prominent part. Since the headaches were associated with bilateral pulsating exophthalmos, Bifulco's patient was hospitalized for cerebral angiography which failed to disclose the suspected aneurysm. At the time of his report the exophthalmos had completely receded although pulsation of the right eye persisted. The exact nature of this mechanism is not apparent. However, the absence of an aneurysm, the recession of the exophthalmos, and the disappearance of the pulsation of the left eye since the withdrawal of vitamin A indicate a causal relationship.

In the case here reported the primary manifestations were headache, blurred vision, diplopia and nausea. These led to a diagnosis of serous meningitis, a condition of increased intracranial pressure considered to be due to thrombosis of the dural venous sinuses secondary to infection or, more rarely, trauma;[52] at times there has been no apparent etiology for the condition and Davidoff and Epstein[53] reported a series of cases which occurred mainly in young people with a history of infection of the middle ear or mastoid. When our patient was first seen by us the subtemporal decompression which had been done to relieve the suspected serous meningitis was still tense and bulging. Ten weeks after the excessive vitamin A intake was stopped, the decompression was completely soft. If she is to be considered to have had serous meningitis, vitamin A toxicity must be added to the causes of this condition. We have no knowledge as to whether dural vein thrombosis was present in this case but there is enough evidence to show that either excess production or decreased absorption of spinal fluid results from vitamin A toxicity. No other explanation can account for the persistence of a tense bulging decompression until vitamin A excess was stopped. The transient episode of diplopia and nystagmus that occurred during her hospital stay took place while her blood level was 444 μg. (more than seven times normal) and therefore while she was still experiencing vitamin A toxicity. The decompression has remained soft and no further cerebral manifestations have occurred since her discharge from the hospital.

SKELETAL MANIFESTATIONS

Our case is the only adult yet reported to demonstrate bone changes. Although bone pains and disability were present in both previously reported adult cases, no x-ray changes were noted in the one case in which they were sought. Radiologic findings in our patient were present in the dorsal and lumbar spine, pelvis, femora, patellae, tibiae, os calcii, scapulae and skull. The fundamental disorder consisted of calcification, with or without true bone formation, of the pericapsular, ligamentous, tendinous and subperiosteal structures. Also noted were decalcification in the skull, scapulae and vertebral bodies. The periosteal changes were the same as observed in the cases of hypervitaminosis A in children. The bone changes were far more extensive, however, probably due to the longer period of toxicity. Biopsy of the tibial tubercle of our patient showed thickened periosteum with secondary calcification. These findings are similar to those of Rineberg and Gross[54] whose biopsy of a child's fibula "showed a strip of newly formed, poorly calcified bone of coarse fibered structure such as is usually seen in ordinary productive periostitis." Six months after vitamin A intake was stopped the child's x-rays showed the subperiosteal calcification to have completely disappeared.

Except for those changes found in the spine of our patient, no similar alterations are demonstrated by any other disease. The spine changes had been diagnosed as Marie-Strümpell arthritis during a previous hospitalization elsewhere. In our opinion there are marked differences between the two conditions. In Marie-Strümpell arthritis the sacroiliac joints are usually involved early and progress with the disease; the anterior spinal ligaments show extensive calcification; there is progressive osteoporosis of the vertebral bodies; calcification of the ligamenta flavae is absent; and clinical improvement occurs slowly, if at all, with therapy.[55] On the other hand, in hypervitaminosis A we have noted that the sacroiliac joints are spared; that only minimal calcification of the anterior spinal ligament occurs; that there is only minimal decalcification of the vertebral bodies; that the ligamenta flavae are calcified; and probably most important, clinical improvement is marked and rapid upon the discontinuance of excessive vitamin A intake.

The marked decalcification of the scapulae

may be related to the high excretion of calcium in the urine. This in turn may be the result of hypervitaminosis A or inactivity.

Studies made in our patient at the time of discharge from the hospital revealed no radiologic improvement in spite of her marked clinical improvement. It is known that in children there is reversibility of the bone findings although these lag far behind the disappearance of symptoms. It is too early to know whether a similar return to normal will occur in our case.

The mechanisms that are responsible for the bone changes in our patient are uncertain. Wolbach[56] found acceleration of epiphyseal cartilage cell growth and maturation of the remodeling processes involved in bone growth in the course of his animal experimentation with hypervitaminosis A. There was accelerated periosteal bone formation in some areas whereas in others there was accelerated resorption of bone with osteoclasis. He found no cause for these changes in the parathyroids, thyroids, adrenals or pituitaries of his animals and concluded that the changes were probably due to a local vitamin A effect. Fell and Mellanby[57] subsequently demonstrated by means of tissue culture that the changes in bone were a direct effect of vitamin A locally. In our case the high blood level of vitamin A would favor the transportation of larger amounts of vitamin A than would otherwise occur.

DERMATOLOGIC MANIFESTATIONS

Dermatologic reactions to excessive intake of vitamin A have been reported consistently in both the acute and chronic states. Polar explorers who ate bear liver had peeling of the skin as early as two days after the high vitamin A repast. Associated with other symptoms and signs of toxicity in animals were skin lesions which ranged from disheveled fur to alopecia, seborrhea, exfoliation, hemorrhagic dermatoses and dry, cracked mucous membranes.

In the chronic intoxication of humans, pruritus is an early and often severe symptom. Fissuring and soreness at the corners of the mouth may appear and disappear in spite of continued use of vitamin A. Coarsening of the skin and alopecia are reported by almost all observers. Loss of the fine lanugo hairs of the extremities is also occasionally noted. Pigmentation of localized areas of skin was noted first by Sulzberger and again by Bifulco. In our patient pigmentation of some areas of skin was so marked that Addison's disease had been considered.

Our patient had suffered all of the skin manifestations cited during the prolonged course of her illness. Because disease of the skin was the initial reason for vitamin A therapy, the changes that took place during the course of toxicity were overlooked. Pruritus and thick, scaling, cracking palmar skin were the most distressing dermatologic manifestations of vitamin A toxicity.

The mechanisms responsible for the skin manifestations are far from clear. As to the pigmentation in our patient, we believe that it was probably secondary to the continued trauma of severe pruritus. The pigmentation was most marked over the abdomen and back where scratch marks were most evident during the early days of her last hospitalization. Biopsy of the skin of the abdomen showed hyperkeratosis and marked pigmentation.

Sulzberger considered hypovitaminosis A and hypothyroidism in the differential diagnosis because of the similarity of their dermatologic findings to those of hypervitaminosis A. That a definite antagonism exists between vitamin A and thyrotropic hormone has been established by animal experimentation.[58] In our patient two basal metabolic determinations made in the early days of her present hospital admission were recorded as plus 12 and plus 10. However, during this period the bone pains were so severe that one could question whether she was in a truly basal state. The protein-bound iodine was repeatedly lower than normal during the present hospital admission. The radio-active iodine uptake three weeks after discharge from the hospital was normal. Our case does not substantiate or deny the thyroid relationship found in experimental studies with vitamin A.

Two and a half weeks after withdrawal of vitamin A excess, pruritus had completely disappeared. In one month the texture of the skin had improved. In two and a half months, lanugo hairs reappeared, the eyebrows became heavier and the scalp hair was more profuse. Pigmentation was not altered.

HEMORRHAGIC MANIFESTATIONS

Hemorrhage is a prominent feature of vitamin A intoxication in animals and often leads to death even in the absence of trauma. The hemorrhages were shown by Light et al.[59] to be the result of hypoprothrombinemia and were controlled by the simultaneous administration

of vitamin K. No consistent hemorrhagic phenomena have been observed in children although sporadic instances of epistaxis were noted. The child reported by Josephs had a post-tonsillectomy hemorrhage. No abnormal bleeding was found in the adult patient reported by Sulzberger, while Bifulco's patient had a severe hemorrhage following dental extractions. These were empirically treated with vitamin K and the bleeding was controlled. There were no studies to ascertain the mechanism for these hemorrhages. In our patient there were no hemorrhagic manifestations. Her menstrual cycle was consistently normal, and she underwent dental extractions, bone biopsy and skin biopsy without excessive bleeding. Studies of prothrombin levels, prothrombin consumption, blood platelets, bleeding and coagulation time were all normal.

SUMMARY AND CONCLUSIONS

A case of chronic hypervitaminosis A in a twenty-eight year old white female is described. Over a period of eight and a half years she was hospitalized ten times because of complaints referable to vitamin A intoxication. Many diagnoses had been made, including brain tumor, serous meningitis, chronic encephalitis, viral radiculoencephalitis, psychoneurosis and generalized infectious arthritis. Her bizarre clinical picture led to additional investigations to exclude Addison's disease, dermatomyositis and hepatitis. In an effort to provide symptomatic relief many measures had been undertaken. These included a subtemporal decompression for the relief of increased intracranial pressure, the application of body spicas, fever therapy, radiotherapy and physiotherapy. During this entire period our patient was allowed to continue the daily consumption of 500,000 units of vitamin A because of the supposed beneficial effects on "ichthyosis" of the skin.

When the clinical diagnosis of hypervitaminosis A was finally proposed, a fasting vitamin A blood level of 2,000 μg. per 100 cc., the highest ever recorded, was disclosed.

Daily estimations of the total vitamin A, including the free alcohol and ester fractions, were made over a period of two and a half months. The influence of menstruation, surgery, cortisone, starvation and alcohol consumption was noted. Stimulated by previous reports concerning the relationship of vitamin A to nephrolithiasis, determinations of the blood levels and urinary excretion of calcium, phosphorus and citric acid were made. Blood analysis for phospholipid phosphorus, total fatty acids, and total lipids were carried out because of their role in vitamin A metabolism. Blood carotene levels were studied to emphasize their independence of the vitamin A levels attained by the ingestion of pure vitamin A.

The clinical manifestations of chronic vitamin A toxicity are reflected in the neurologic, skeletal and dermatologic systems. Persistent, severe headache with visual disturbances in the absence of focalizing neurologic signs may occur in hypervitaminosis A. This is the result of increased intracranial pressure due to excessive production or decreased absorption of cerebrospinal fluid. In our patient a subtemporal decompression had been performed elsewhere after a diagnosis of serous meningitis had been made.

Bone pains are usually present in chronic vitamin A intoxication. X-ray evidence of bone involvement has not been previously described in adults. In our case x-ray and bone biopsy studies indicate that the fundamental disturbance consists of calcification with or without true bone formation in the pericapsular, ligamentous, tendinous and subperiosteal tissues. The pain and the progressive crippling deformities in our patient had been previously considered the results of generalized infectious arthritis. The differences between Marie-Strümpell arthritis and vitamin A toxicity are discussed in detail.

The dermatologic manifestations of vitamin A toxicity include pruritus, fissuring and soreness at the corners of the mouth, coarsening of the hair with alopecia, loss of the fine lanugo hairs of the extremities and pigmentation.

Hemorrhagic manifestations during vitamin A toxicity have been considered by others to be of clinical significance. Our patient failed to show any hemorrhagic tendencies. Laboratory studies likewise showed no disturbance in any of the factors related to the clotting mechanism. Because of interest in the relationship of vitamin A to thyroid activity tests were made of the basal metabolism, protein-bound iodine and radioactive iodine uptake. These showed no consistent pattern of altered thyroid activity.

Clinical improvement in the neurologic, skeletal and skin manifestations took place rapidly upon stopping excess vitamin A intake.

This rapid response is a most important point in the differential diagnosis.

Treatment with massive doses of vitamin A now recommended in many clinical conditions must be reviewed from the standpoint of potential toxicity. If these large doses are to be used, rest periods should be instituted and determinations of the vitamin A blood level made. Self-medication with vitamin concentrates containing large doses of vitamin A is a common occurrence due to the general belief by the laity that vitamins improve health and increase resistance to infection.

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Atypical Amyloidosis and Bone Marrow Plasmacytosis in a Case of Hypersensitivity to Sulfonamides*

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THE occurrence of atypical amyloidosis, hyperglobulinemia and bone marrow plasmacytosis in multiple myeloma is well known. In the case to be presented this triad occurred in the absence of multiple myeloma. The basic pathogenetic mechanism underlying the clinical and pathologic picture in this case would seem to be a hypersensitive state due to a sulfonamide. Such an occurrence is unusual and permits speculation as to the relationship of these three findings to each other and to hypersensitivity.

CASE REPORT

A fifty-five year old white salesman was well until July 8, 1950, when he developed abdominal cramps and diarrhea which were thought to be due to "food poisoning." He was treated with 0.5 gm. gantrisin®† three times a day. The diarrhea stopped after three days and the drug was discontinued. However, three days later the diarrhea recurred and therapy with the same drug was resumed. The following day the patient developed vesicles on the palms of the hands and the soles of the feet. Sulfonamide therapy was continued for a period of about two months and during this period there were recurring crops of vesicles on the hands, arms, feet and legs.

His past history was significant in that he had had pneumonia in January, 1950, and was treated with penicillin and sulfadiazine. In June, 1950, examination including urinalysis was normal.

† 3,4-dimethyl-5 sulfanilamido-isoxazole.

In September, 1950, his physician noted widespread vesicular and bullous lesions arising from apparently normal skin. When pressure was made on these lesions, the fluid spread out easily beneath the adjacent skin. It was difficult to rupture the bullae because of this spreading effect. The fluid was turbid but not purulent. The lesions were present in the skin of the scrotum, groin and axillas as well as the extremities. Nikolski's sign was positive. At this time a persistent albuminuria was noted. The serum albumin was 2.8 gm. and the serum globulin 4.7 gm. per 100 cc. Examination of a sternal marrow smear revealed marked plasmacytosis, 50 per cent of all the nucleated cells being plasma cells. Because of this finding and the hyperglobulinemia a diagnosis of multiple myeloma, complicated by pemphigus vulgaris, was made. The patient received a total of 520 mg. ACTH without any effect. He was transferred to the Bronx Veterans Administration Hospital on November 24, 1950.

On admission several large bullae were present on the dorsum of the right foot and heel, together with numerous widely scattered crusted and oozing skin lesions. Depigmented scars were noted in the skin of the scrotum and buttocks at the sites of previous vesicles and bullae. Otherwise the physical examination was entirely within normal limits. The blood pressure was 110/60. The highest specific gravity of the urine on several concentration tests was 1.020. There was a 4+ proteinuria and a total of 7.39 gm. of protein in one twenty-four-hour urine specimen. The urine sediment showed hyaline casts, 2 to

* From the Medical and Laboratory Services of the Veterans Administration Hospital, Bronx, N. Y. Read by title at the Forty-Ninth Annual Meeting of the American Association of Pathologists and Bacteriologists, New York City, April 10, 1952.

4 red blood cells and 5 to 10 white blood cells per high power field. At least twenty determinations for Bence-Jones protein were made and all were negative. No uroporphyrins were found in the urine. There was 15 per cent P.S.P. excretion in fifteen minutes; the urea clearance was normal. The blood urea nitrogen averaged 18 mg. per 100 cc. There was a mild anemia (hemoglobin 10.8 gm. and 3.5 million red blood cells per cu. mm.). The leukocyte count and differential were normal and the sedimentation rate 36 mm./hour (normal up to 15 mm./hour). Serologic tests for syphilis were negative. The total cholesterol was 236 mg. per 100 cc. with 70 per cent esters. Cephalin flocculation and thymol turbidity tests were normal. The serum calcium, phosphorus and alkaline phosphatase were normal. The total plasma protein was 7.6 gm. per 100 cc. with 2.6 gm. of albumin and 5.0 gm. of globulin. Electrophoretic studies indicated that the increase in the globulin was largely in the alpha fraction. There were no cryoglobulins. Twenty-six per cent of injected Congo red dye was absorbed at the end of one hour. X-ray examination of the entire skeletal system was normal. Intravenous pyelogram, x-rays of the chest and electrocardiograms were negative. A sternal marrow smear confirmed the previously observed plasmacytosis. The total count was 91,000 nucleated cells per cu. mm.; 40 per cent of the nucleated cells were mature plasma cells and an additional 5 per cent were plasmablasts which were considered by the hematologists to be "myeloma" cells. A skin biopsy of one of the vesicles was made on November 28, 1950, and the pathologic report was "either dystrophic epidermolysis bullosa or pemphigus." The pathologist favored the latter diagnosis.*

The patient felt well despite recurring crops of vesicles and bullae on the soles of the feet, palms of the hands and scrotum. There were no mucous membrane lesions. A test dose of sulfasuxidine seemed to accelerate the appearance of the skin lesions, although it was difficult to be certain of this because of their irregular and intermittent recurrence. A bone marrow smear in February, 1951, showed 38 per cent plasma cells with "typical myeloma" cells. Another complete roentgenographic survey of the skeletal system was negative. The serum globulin remained elevated (average of 5.2 gm. per 100 cc.). His anemia did not respond to iron and he began to have short unexplained febrile episodes.

He was discharged in March, 1951, only to return in a month with many more bullae and complaining of exertional dyspnea. At no time did he complain of bone pain. Because of low grade fever due to secondary infection of the skin lesions he was treated with aureomycin and chloramphenicol, with control of the pyogenic infection. A third bone marrow smear on April 30, 1951, showed 55 per cent plasma cells. (Fig. 1.) This was the last bone marrow study, approximately six months before death. The serum globulin was 5.0 gm. per 100 cc.; the albuminuria and anemia continued. A third x-ray survey of the skeletal system was negative for any changes.

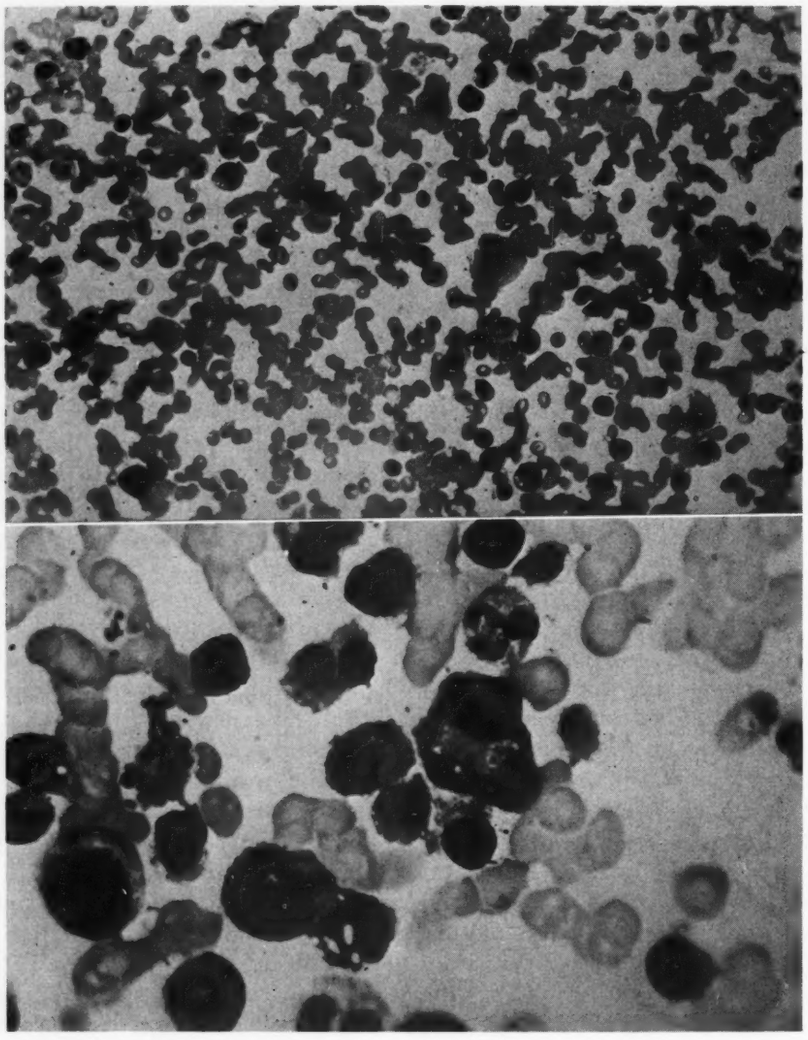
He began to feel weak and complained of anorexia, nausea and abdominal pain. No adequate cause could be found for these complaints. Shortly after this last admission in April, 1951, he experienced a sudden pain in the right occipital area, lasting about an hour. The next day he was found to have superior right homonomous hemianopsia which cleared within three weeks. The electroencephalogram and spinal fluid were normal.

In June, 1951, the patient suffered an episode of severe constricting anterior chest pain, relieved by nitroglycerin. The electrocardiographic changes suggested an anteroseptal myocardial infarct. He recovered sufficiently within five weeks to be allowed out of bed but experienced angina on slight exertion. The recurrent bullous eruptions continued. The anemia, albuminuria and hyperglobulinemia persisted.

Late in August, 1951, he suddenly lapsed into unconsciousness. On regaining consciousness he was found to be aphasic and there was a left hemiplegia. He recovered only slightly from this episode, developed hyperpyrexia and died on October 9, 1951. The total duration of illness was fifteen months.

Postmortem examination was performed three hours after death. There were numerous vesicular and bullous lesions of the skin of the face, back, lower extremities and soles of the feet. Several of the larger bullae measured up to 3.0 cm. in diameter and contained a turbid yellow fluid. The tongue was not enlarged and presented no gross abnormalities. The mucous membranes of

* The patient was presented at the Manhattan and the Atlantic Dermatologic Societies on January 9, 1951, and March 3, 1951. *Arch. Derm. & Syph.*, 65: 241, 503, 1952.



1A

1B

FIG. 1. Bone marrow smear made on April 30, 1951. The number and characteristic appearance of the plasma cells are shown. A, × 264; B, × 1190.

the mouth, nasopharynx and the conjunctivae were negative. There was bilateral hydrothorax and focal fibrinous pericarditis. The heart was enlarged (weight 500 gm.) and both ventricles were moderately hypertrophied. There was widespread fibrosis and focal necrosis of the myocardium of the left ventricle and fibrous replacement of the interventricular septum in its anterior apical portion. The left coronary artery and its main branches were slightly atherosclerotic and widely patent; the right coronary artery showed moderate thickening and narrowing of the lumen but was patent throughout its entire course. The leaflets of the mitral and tricuspid valves were somewhat distorted by clusters of small subendocardial nodules, most prominent along the margins of closure. The aortic and pulmonic valves were grossly negative. The endocardium of both atria was diffusely thickened and opaque yellowish-gray. Mural thrombi were present in both auricular appendages, some partly organized and others fresh and loosely attached. The lungs were greatly increased in weight due to marked congestion and edema. Large hemorrhagic subpleural infarcts were present in the bases of both lower lobes as a result of embolic occlusion of the appertaining branches of the pulmonary arteries. The esophagus was negative. Extensive mucosal and subserosal hemorrhages were noted throughout the stomach, the small and large intestine and rectum. The liver, gallbladder and biliary duct system were not remarkable. A small fibrotic cortical infarct was found in the right

kidney; the genitourinary tract was otherwise normal. The spleen was of average size and weight, soft and flabby, the pulp pale red and the malpighian corpuscles distinct. An old subcapsular infarct was seen at the lower pole. The adrenals, thyroid gland, the skeletal musculature and adipose tissue were not remarkable. The thoracic lymph nodes were enlarged and many of the tracheobronchial nodes measured 2.5 cm. or more in greatest dimension. The cut surface was smooth, grayish-yellow and translucent. The cervical, abdominal and retro-aortic nodes were not appreciably enlarged. Section through the lumbar, thoracic and cervical vertebrae revealed normal bone structure and a dark red marrow. Nowhere could bone destruction or osteoporosis be detected. Multiple sections through the sternum, ilium, ribs and skull likewise disclosed grossly normal bone structure and marrow. The brain showed a massive infarct of the right cerebral hemisphere. Section of the brain revealed fresh encephalomalacia of both frontal lobes, the right parietal, temporal and occipital lobes and the basal ganglia bilaterally. The right internal carotid artery, just proximal to its middle cerebral branch, was occluded by a firmly adherent embolus. The caliber of the left internal carotid artery was greatly narrowed, apparently on a congenital basis, but was patent and thin-walled.

One of the most striking features on microscopic examination of the tissues was the extensive and widespread deposition of amyloid in the medium-sized arteries and the arterioles. Virtually all such vessels in the skin, skeletal musculature, adipose tissue, heart, lungs, thyroid gland, esophagus, gastrointestinal tract, liver, gallbladder, spleen, pancreas, adrenals, kidneys, urinary bladder, prostate, epididymides, testes, lymph nodes, bone marrow and the pituitary body were converted into greatly thickened tubes of amyloid with narrowed lumens. The amyloid infiltration of the small arteries was often accompanied by a fibroblastic proliferation in the intima, which further narrowed their lumens. These alterations were most advanced in the small coronary arteries, many of which were nearly occluded. (Fig. 2.) In addition, the small amyloidotic arteries showed variable damage to the internal elastic membrane. Frequently the elastic lamellae presented a beaded appearance as a result of fragmentation of part or all of the membrane. There was also fraying, thinning, reduplication and, in some instances,

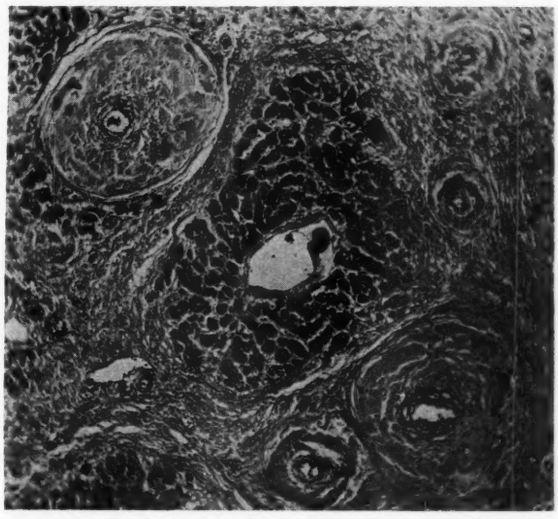


FIG. 2. Heart, left ventricle. Marked thickening of medium-sized coronary arteries and arterioles by deposition of amyloid, with extreme narrowing of lumens. Extensive atrophy and fibrosis of myocardium, with small islands of well preserved muscle; hematoxylin and eosin stain, × 150.

disappearance of major portions of the internal elastica. Again, these changes were most conspicuous in the small coronary arteries. Everywhere the small veins were slightly to moderately thickened by amyloid deposition but there was no appreciable reduction in their caliber. All the blood vessels in the meninges, the brain and the spinal cord were free of amyloid. The large arteries and veins throughout the body were also spared.

In the heart, apart from the small coronary arteries, amyloid was seen mainly in the endocardium and in the valves. Only a few small foci of amyloid could be detected in the myocardium and in the epicardial fat. Each leaflet of all four valves contained variable but small deposits of amyloid in the form of narrow bands and nodules. The most prominent deposition was in the mitral valve and produced the deformation seen grossly. The endocardium of both atria was massively infiltrated with amyloid but the ventricular endocardium showed only minimal focal deposition. (Fig. 3.) The elastic fibers of the atrial endocardium had undergone extreme fragmentation and disruption similar to that seen in the internal elastica of some of the small coronary arteries. The myocardium presented a variegated appearance, with intermingled foci of acute necrosis, ischemic atrophy and fibrosis separating small and large islands of well preserved myocardium.

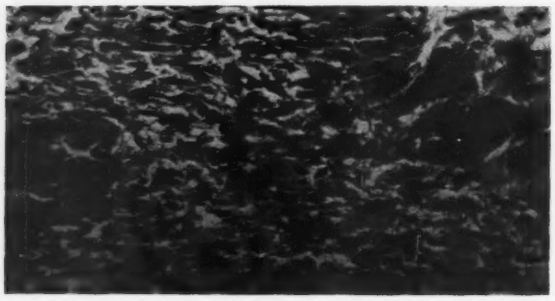


FIG. 3. Masses of amyloid in endocardium of left atrium. Marked fragmentation and disruption of elastic lamellae. Verhoeff's stain for elastic fibers, counterstained with van Gieson's stain, × 475.

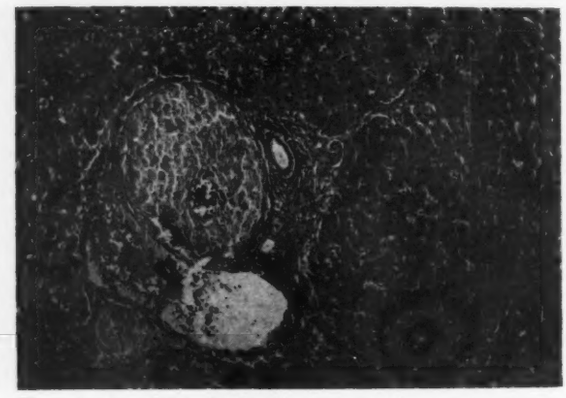


FIG. 4. Amyloid thickening of arteries and vein in portal space; parenchyma of liver free of amyloid, × 100.

In the lungs many of the alveolar septa and the muscle layers of bronchi were thickened by amyloid infiltration. Amyloid was also present in the capsule and trabeculae of the spleen, the skeletal musculature, the muscle of the urinary bladder, the fibromuscular stroma of the prostate, the muscularis mucosae and muscle layers of the esophagus and the entire gastrointestinal tract. The thoracic lymph nodes were replaced, for the most part, by amyloid with only small remnants of lymphoid tissue preserved.

No amyloid could be detected in the parenchyma of the liver, spleen or the adrenals. (Fig. 4.) However, deposition of amyloid was present in the glomeruli of the kidneys, varying in degree from several small spherules in the capillary tufts to replacement of the entire glomerulus. (Fig. 5.) Occasionally Bowman's capsule was thickened by amyloid. Hyaline granules were prominent in the epithelium of many of the proximal convoluted tubules, and hyaline casts often filled the collecting tubules. The afferent arterioles, the interlobar and the

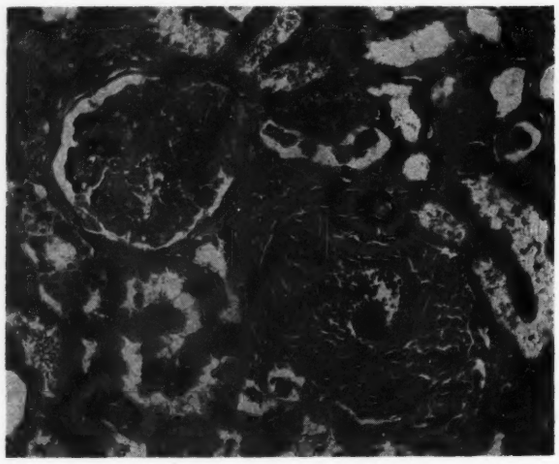


FIG. 5. Amyloid deposition in glomerular tufts and interlobular artery of kidney; hematoxylin and eosin stain, × 100.

arcuate arteries of the kidneys were all markedly thickened by amyloid.

Numerous sections of the skin disclosed extensive amyloid infiltration of the dermis, including some of the sebaceous glands, hair follicles and arrectores pilorum. Vesicles were seen between the dermis and epidermis, with cleavage at the dermo-epidermal junction. There was no inflammatory cellular reaction in the dermis at the base of the vesicles.

In view of the atypical amyloidosis found in the postmortem material, sections of the skin biopsy obtained on November 28, 1950, were re-examined and special stains demonstrated amyloid in the dermis and in the arterioles and veins.

Many sections of the vertebrae, sternum, ribs, skull and ilium revealed normal bone structure and normal bone marrow. There were no signs of erosion or necrosis of bone trabeculae. Scattered among the marrow elements were a few plasma cells. The virtual absence of plasma cells in the bone marrow and in any of the organs and the absence of bone destruction definitely excluded multiple myeloma.

The gray and white matter of the brain and spinal cord, the nerve trunks, peripheral nerves and the ganglia were free of amyloid deposition.

The amyloid in the hematoxylin- and eosin-stained sections appeared as an amorphous, homogeneous pink-staining material. The amyloid stained metachromatically with crystal violet, pink to red with Congo red, and greenish-yellow with Van Gieson's stain.

The final major diagnoses were: Atypical

amyloidosis; focal necrosis, ischemic atrophy and fibrosis of myocardium; fibrinous pericarditis; bilateral hydrothorax; mural thrombi, right and left auricular appendages; infarcts in lungs, left kidney and spleen; embolus occluding right internal carotid artery; massive infarct right cerebral hemisphere; pemphigus.

COMMENT

In 1929 Lubarsch[1] focused attention on a rare form of amyloidosis which was not associated with chronic infections and which involved the skin, smooth and striated musculature and blood vessels. The parenchymatous organs were spared in this type which he designated atypical amyloidosis. In 1933 Strauss[2] collected thirty-three such cases from the literature, emphasized the selective deposition of amyloid in the mesenchymal tissues and suggested the term paramyloidosis for this form. Teilum[3] introduced the expression hyalinosis, a term he uses interchangeably with paramyloidosis. Reiman, Kouky and Eklund[4] designated this same form as primary amyloidosis and further classified the other amyloid states into secondary amyloidosis (complicating chronic infection); tumor-forming amyloid; and amyloidosis associated with multiple myeloma. In the last group the distribution of the amyloid is similar to that seen in atypical amyloidosis, and occurs in about 7 per cent of cases of multiple myeloma.[5]

To date about eighty-five cases of atypical amyloidosis have been recorded. Comprehensive reviews, with tabulations and analyses of these cases, have been published by Strauss;[2] Koletsky and Stecher;[6] Reiman, Kouky and Eklund;[4] and Iverson and Morrison.[7]

The present case is an example of atypical amyloidosis in which there was selective deposition of amyloid in tissues of mesodermal origin and absence of amyloid in the parenchyma of the liver, spleen and the adrenals. However, amyloidosis of the glomeruli of the kidneys did occur and as a result our patient developed a nephrotic syndrome. While amyloid deposition in the glomeruli and consequent development of the nephrotic syndrome are common in secondary amyloidosis, such an occurrence is rare in atypical amyloidosis. In the latter, the glomeruli are, as a rule, spared. Lindsay[8] has reported a case of his own, and refers to three additional cases in the literature, in which a nephrotic syndrome occurred in primary (atypical) amyloidosis. In a comprehensive discussion of the nephrotic states, Allen[9] clarifies the basic mechanism concerned in the production of the nephrotic syndrome. He emphasizes that it is the glomerular damage in amyloidosis and not the tubular changes which accounts for the nephrotic picture.

Another unusual feature in our case was the severe damage to the elastica in the blood vessels and the atrial endocardium. Eisen[10] also has described partial destruction and reduplication of the internal elastic membrane of the arterioles in one of his cases of primary amyloidosis. It is worth noting, however, that similar changes may also occur in the internal elastica of small arteries, which occasionally are infiltrated in cases of secondary amyloidosis. In two such cases observed in this laboratory, one complicating pulmonary tuberculosis and the other chronic pyelonephritis, the internal elastica showed distinct fragmentation.[11] Josselson, Pruitt and Edwards,[12] in a study of amyloidosis localized in the heart, also observed damage to the elastica of the atrial endocardium but the extreme disruption and fragmentation of the elastic laminae in the present case is unique. These authors found, as occurred in our case, a preponderant amyloid infiltration of the atrial as compared with the ventricular endocardium.

In many of the reported cases of atypical amyloidosis the clinical picture was dominated by progressive and intractable heart failure. At necropsy such cases have generally shown massive replacement of the myocardium or extensive deformity of valves by amyloid deposition. In the present case there was only minimal amyloid in the myocardium and in the valve leaflets. The marked narrowing and occlusion of the amyloidotic medium-sized coronary arteries and the arterioles produced widespread ischemic atrophy, necrosis and fibrosis of the myocardium which were the basis for the electrocardiographic changes, precordial pain and heart failure.

That bone marrow plasmacytosis may occur in diseases other than multiple myeloma should be emphasized. Fadem and McBirnie[13] reported six cases (other than multiple myeloma) in which there was a bone marrow plasmacytosis as high as 26 per cent. Wells[14] has reported an instance in which the bone marrow plasmacytes reached a level of 50 per cent in the absence of multiple myeloma. Bing,[15] Bayrd,[16] Carter[17] and Robertson[18] have reported bone marrow plasmacytosis in such diverse diseases as Hodgkin's disease, measles, Boeck's sarcoid, carcinoma,

polyarteritis nodosa, cirrhosis of liver, kala azar, lymphopathia venereum, syphilis and the hypersensitive state. In addition to the increased number, there were also qualitative changes in the plasma cells in our case of a type that has usually been interpreted as diagnostic of multiple myeloma. Many hematologists believe that while an increase in the total number of plasma cells in the marrow is no longer diagnostic of myeloma, the presence of immature plasma cells which have been designated "myeloma cells" is specific and establishes the diagnosis.[19] Three hematologists unequivocally identified "myeloma cells" in our patient's marrow. However, the absence of plasma cells in any of the organs or in the bone marrow at autopsy and the lack of bone necrosis eliminates the possibility that this patient had multiple myeloma, in our opinion. Immaturity of the plasma cells in the bone marrow is a reflection of the intensity of the stimulus evoking the plasmacytic response and does not necessarily indicate the presence of multiple myeloma. At this hospital we have found "myeloma cells" in bone marrow smears of patients who had a marked plasmacytosis but who did not have multiple myeloma. The present case is an example of our experience. The transient nature of the plasmacytosis, which was found only through a period of eight months, is of additional interest.

The clinical picture of the present case can best be explained as due to an allergic or hypersensitive response to gantrisin. A provocative test with sulfasuxidine did seem to cause an increased formation of vesicles and bullae. As will be discussed later, this type of skin eruption has been seen in hypersensitive responses to sulfonamides. The intense, although transient, plasmacytosis with the so-called "myeloma cells" can also be ascribed to such a hypersensitive reaction. The hyperglobulinemia and amyloidosis, we believe, are part of a similar response. This patient may have become sensitized to sulfonamides when he was treated for pneumonia with sulfadiazine six months prior to taking gantrisin. It is also possible that gantrisin itself was the sensitizing agent since the first signs of the rash appeared seven days after he started to take this drug. With the mistaken idea that the eruption was due to an infection, the patient on his own continued to take the drug for two more months. The rash persisted after the medication was discontinued. This is not unusual since the hypersensitive process, once started, may no longer require continuing administration of the sensitizing agent.

The early appearance of the hyperglobulinemia, bone marrow plasmacytosis and amyloidosis is of interest. The first two were present two months after the appearance of the vesiculobullous eruption. Since proteinuria was also present at the same time, it is reasonable to assume that amyloid was already being deposited in the glomeruli. The marked plasmacytic response so early in his illness is at variance with Robertson's[18] suggestion that the appearance of plasma cells might be an indication of relative chronicity in the development of the responses to the hypersensitive state.

The triad of atypical amyloidosis, plasmacytosis and hyperglobulinemia occurs in about 7 per cent of cases of multiple myeloma. However, there have been three cases reported of these three findings occurring together in patients suffering from a hypersensitive reaction. The present case makes the fourth such instance. Teilum[20] reported a patient who died with atypical amyloidosis in whom during life there was bone marrow plasmacytosis and hyperglobulinemia. This man's last illness began twenty months prior to his death when he took sulfonamide for a pneumonic infection. The author felt that the clinical and necropsy findings were due to sensitization to the sulfonamide. He further remarked that he had seen another such case. Ritama and Saksela[21] described a case with the same triad. This man had had numerous infections during his lifetime. The suggestion was made that the patient had become sensitized to the toxins of his repeated infections. Although no mention was made of the therapy used, he was ill during the sulfonamide era and may have received at least one of the sulfonamide drugs. Wells[14] reported a third case with the same combination of findings. The bone marrow plasmacytosis was as high as 57 per cent but was transitory and not found at autopsy. Wells also believed that this triad was due to a hypersensitive response. This man did not give a history of sulfonamide ingestion. In all three of these cases multiple myeloma was considered clinically and was excluded by autopsy findings.

While there have been excellent reviews of the pathologic changes seen in hypersensitive reactions to sulfonamides, none mentions the occurrence of amyloidosis or plasmacytosis.[22–25] Robertson,[18] however, reported two cases of plasmacytosis and hyperglobulinemia occurring

as part of a hypersensitive response. It seems clear that sulfonamide hypersensitivity was responsible for his first case while the probable antigen in the second case is not apparent. Both of these cases showed a marked plasmacytic infiltration of most of the organs of the body at autopsy.

There is good experimental and clinical evidence that plasmacytosis and hyperglobulinemia are related to hypersensitive responses to a variety of stimuli. The plasma cell is probably concerned with antibody formation and production of abnormal globulins.[26] This would account for its presence in a variety of chronic illnesses as well as in the hyperimmune state. In most cases, as has been pointed out by Bing and Plum,[27] hyperglobulinemia is also present but in others there may be qualitative alterations in the globulin rather than an increase in amount. In some cases hyperglobulinemia has been found without plasmacytosis. The fact that in our case the plasmacytosis was transitory and disappeared completely, although the hyperglobinemia persisted, may be helpful in clarifying the relationship between the two. Kolouch,[28] Kolouch, Good and Campbell[29] and Bjoerneboe and Gormsen[30] demonstrated that plasma cells appeared in large numbers in the bone marrow and spleen of rabbits immunized or hyperimmunized with a variety of antigens. Bjoerneboe, Gormsen and Lundquist[31] correlated the rise in antibody titer with the increase in plasma cells. Good and Campbell[32] found a tenfold increase of the plasma cells in the bone marrow of patients in the acute phase of rheumatic fever. The number of plasma cells paralleled the rise in serum gamma globulin. Carter's[17] case furnishes further evidence of the relationship of hyperglobulinemia and plasmacytosis to the hypersensitive process. His patient became sensitized to trichinella and developed hyperglobulinemia and at necropsy showed bone marrow and tissue plasmacytosis. Robertson's[18] cases, previously mentioned, are still other examples of hypersensitization evoking a plasmacytic response with hyperglobulinemia.

It appears, then, that hyperglobulinemia and plasmacytosis may be related to the hypersensitive process. While hyperglobulinemia ordinarily occurs in many diseases without any evidence of amyloidosis, it is a usual finding in patients with secondary amyloidosis. It is not commonly found associated with primary amyloidosis except in multiple myeloma. There is, however, experimental evidence that hyperglobulinemia is related also to atypical amyloid and that both may be related to the hyperimmune state. That hyperglobulinemia may appear together with amyloid disease was noted by Jaffe[33,34] in 1926. Letterer[35] also noted this combination and believed that the increase in globulin was the primary basis for amyloid disease. However, the relationship to hypersensitization became clear when Sipos and others[36–38] found that hyperimmunized horses which had been used in the commercial production of vaccines frequently developed hyperglobulinemia and atypical amyloidosis. Dick and Leiter[39] produced the same combination in rabbits by injection of streptococcal antigens. Reiman and Eklund[40] similarly produced hyperglobulinemia and amyloidosis by sodium caseinate injections. Haas[41] suggested that persistent or repeated stimulation of the immune mechanism was the fundamental factor in the genesis of amyloid. It would seem, therefore, that hyperglobulinemia and amyloidosis are related to each other and that both are related in some fashion to the immune and allergic states and one would expect to find all three responses occurring in a single individual suffering from hypersensitivity. The cases of Teilum,[20] Ritama[21] and Wells[14] together with the present case are such examples. Barr[42] had previously posed this question: "Is it possible that many of the cases of diffuse myelomatosis, classified in the literature as myeloma, and regarded as examples of malignant new growth, represent an immunologic response engendered by as yet unknown stimuli and characterized by an excessive plasma cell response and the production of sometimes large amounts of immune globulin?" These four cases which have been mentioned now make this problem more pertinent.

The skin eruption adds still further weight to our contention that hypersensitivity to sulfonamide was the basic pathogenetic factor in this case. A vesiculobullous eruption very similar to the one which appeared in our case has been reported in hypersensitive responses to sulfonamides. Bloom[43] listed two major types of skin eruptions due to sulfonamides. The first type is primarily a toxic one which usually subsides and does not recur after readministration of the drug. The second type is due to allergy or hypersensitization. An interval of at least seven days must elapse between the drug administration and the appearance of the rash. This reac-

tion may perpetuate itself even after the drug has been stopped. While the usual sulfonamide rash is maculopapular or scarlatiniform in nature, Loveman and Simon[44] described a case with a bullous eruption due to sulfanilamide medication. Wien and Lieberthal[45] reported a patient who developed an exfoliative dermatitis resembling pemphigus foliaceus subsequent to sulfonamide therapy. Bloom reported two patients with vesiculobullous eruptions due to sulfonamide allergy. One case resembled pemphigus vulgaris. Weinstein and Domm[46] had a similar case of a bullous eruption following sulfathiazole.

SUMMARY

A patient who became sensitized to sulfonamides developed atypical amyloidosis, bone marrow plasmacytosis and hyperglobulinemia in the absence of multiple myeloma. The probable relationship of these three findings to each other and to the hypersensitive state is discussed.

It is emphasized that bone marrow plasmacytosis may be a response to hypersensitivity and that such plasmacytosis may lead to an erroneous diagnosis of multiple myeloma. The nonspecificity of immature plasma cells frequently designated "myeloma cells" is noted.

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Hypothromboplastinemia Associated with a Circulating Anticoagulant and Hemorrhagic Diathesis*

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IN 1940 Lozner, Jolliffe and Taylor[1] presented the first documented case of a hemorrhagic diathesis associated with a circulating anticoagulant. Hematologically, the most prominent feature of the case was the presence of a prolonged coagulation time. Since that initial report a total of thirteen cases have been described in the literature.

Conley[2] and Dieter[3] each presented a case of prolonged clotting time associated with a circulating anticoagulant arising spontaneously in a non-hemophiliac male. Munro[4] and Van Creveld[5] reported the phenomenon of the failure of hemophiliac patients to respond to fresh blood or plasma transfusions. All of these patients had responded to previous therapy with a marked reduction in the clotting time. Hewlett and Haden[6] reported two females, seven months and one year postpartum, respectively, with a prolonged coagulation time and a circulating anticoagulant, neither patient having received blood transfusions previously. Dreskin and Rosenthal[7] reported a similar experience in a thirty year old female seven weeks postpartum.

In all cases the coagulation time was significantly prolonged and an anticoagulant was identified. These cases may be divided into three categories; (1) cases in which the anticoagulant arose *de novo;* (2) those which occurred in the postpartum state and (3) those which developed in patients who had previously received multiple whole blood transfusions.

We are presenting the case of a twenty-seven year old female who, three months postpartum, developed her first manifestations of a bleeding tendency. This subsequently became severe and the patient had a massive gastrointestinal hemorrhage. Hematologic studies revealed a markedly prolonged clotting time associated with the presence of a circulating anticoagulant.

CASE REPORT

E. K., a twenty-seven year old housewife, was admitted to University Hospital for the first time on March 25, 1953, with the chief complaint of multiple, painful, "black and blue spots" over her extremities of four months' duration.

The patient had always enjoyed excellent health. In July, 1952, she gave birth to a son without difficulty despite the fact that it was a breech presentation. Four hours after delivery a retained placenta was removed manually. There was no appreciable bleeding noted. One week later the child was circumcized without incident.

One month after parturition the patient experienced a sudden sharp pain in the epigastrium and right upper quadrant. The pain radiated in girdle-like fashion to the right scapula. This cleared but during the next two months the patient experienced many such episodes. A cholecystogram revealed evidence of stones and on October 15, 1952, under spinal anesthesia, elective cholecystectomy was performed without difficulty at another institution.

Initial preoperative blood studies revealed the hemoglobin to be 11.5 gm. per 100 cc. of blood and the erythrocytes 3.89 million per cu. mm. of blood. The leukocyte count was 6,400. The blood type was AB, Rh-positive.

Although there was no evidence of excessive bleeding during surgery, 500 cc. of whole blood was given twenty-four hours later. One hour after the transfusion was begun the patient's temperature spiked to 102.4°F. There was no chill, urticaria or icterus. The patient's course

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was uneventful and on the sixth postoperative day the sutures and drain were removed. Three hours later she began to bleed from the operative site. The blood count was repeated and there was no perceptible change. The platelets numbered 555,800 per cu. mm. of blood. The prothrombin time (Quick) was ten seconds. The bleeding time was thirty seconds and the coagulation time was reported as four minutes. She continued to bleed until the next day and was given 500 cc. of whole blood without incident. Within twelve hours bleeding stopped and did not recur. The patient was discharged four days later with the diagnoses of chronic cholecytitis and cholelithiasis, and bleeding of undetermined etiology.

The patient had a completely uneventful convalescent period, menstruating normally on December 8th. On December 24th she noticed the sudden onset of painful swelling of the right wrist. The next day the left wrist also became swollen and tender. In a few days ecchymoses of both wrists appeared spontaneously and rapidly extended up the volar aspect of the forearms. Later a similar painful ecchymotic area appeared over the entire right ankle and foot, incapacitating the patient. Roentgen examination of the ankle was unrevealing. Three days later the patient had a mild episode of nausea and vomiting; this cleared spontaneously. However, it soon returned and with it the patient suddenly vomited a large quantity of bright red blood. She later passed a copious tarry stool. There were no localizing abdominal symptoms. The patient was readmitted to the hospital as an emergency.

Examination revealed the pulse rate to be 108 beats per minute, the respiratory rate 28 per minute and the blood pressure 120 systolic and 60 diastolic. The physical examination was entirely negative except for painful ecchymotic areas over the left buttock, right foot and both forearms extending into the biceps region. The blood count on admission revealed a hemoglobin of 7.25 gm. per 100 cc. and the erythrocytes 2.8 million per cu. mm. of blood.

An immediate transfusion of 500 cc. of whole blood was given. During the course of this admission a total of 4,000 cc. of whole blood was administered without incident.

Laboratory studies revealed the erythrocyte fragility test to be within normal limits. The bleeding and clot retraction time was normal. The Rumpel-Leedes test was negative. The prothrombin time (Quick) was eleven seconds. The coagulation time (Lee-White) was reported as forty-two minutes. The icteric index was 5 units, the cephalin flocculation test was negative, the total protein was 5.9 gm. with 3.9 gm. of albumin and 2.0 gm. of globulin per 100 cc. of blood. The urinalysis was completely negative. Roentgenographic examination of the stomach revealed evidence of irritability and spasm in the pyloroduodenal segment without evidence of a niche.

The clinical course after the first forty-eight hours was uneventful. New areas of ecchymoses did not appear. On the twelfth hospital day she was discharged. During the next two months ecchymotic areas continued to appear spontaneously over her arms and legs. She received a course of parenteral vitamin K for a short time without apparent effect. Because of the persistence of the patient's hemorrhagic phenomena she was referred to one of us (M. S. B.) for further evaluation and possible therapy. The patient was admitted to University Hospital on March 25, 1953, for that purpose.

A careful evaluation of the family history failed to reveal any evidence of a bleeding tendency in any of its members. The past history was unremarkable except that the patient's menstrual periods lasted up to ten days. There was no history of exposure to known bone marrow depressant chemicals or drugs.

Physical examination revealed the patient to be well developed and well nourished. She did not appear to be acutely ill and was in no distress. The temperature was 99°F., the pulse rate 100 beats per minute, respiratory rate 16 and the blood pressure was 120 systolic and 80 diastolic. There was some oozing of the gums at the base of the lower right premolars. There was no icterus and no petechiae. Large areas of resolving ecchymoses were present over the lateral and medial aspects of the left arm just above the elbow joint and around the right ankle. There was no significant lymphadenopathy. The liver and spleen were not palpable. There were no other significant abnormalities.

Laboratory studies revealed the hemoglobin to be 10.2 gm. per 100 cc. of blood and the erythrocytes 4.10 million per cu. mm. The leukocytes were 5,650 and the differential count was normal. The hematocrit was 41 per cent. The reticulocyte count was 3.7 per cent. The

sedimentation rate (Wintrobe) was 18 mm. per hour. The bleeding time was three minutes, the coagulation time was ninety minutes and the clot retracted in thirty-five minutes. The Rumpel-Leedes test was negative. The prothrombin time (undiluted) was sixteen seconds. The patient's blood typed AB, Rh-positive.

Sternal marrow aspiration was performed. The myeloid-erythroid ratio was 2.2:1. The differential cell count was not remarkable. Normal appearing megakaryocytes producing platelets were frequently seen.

The serum bilirubin was 0.75 mg. per 100 cc. of blood. The total protein measured 6.7 gm. per 100 cc. of blood with 4.0 gm. of albumin and 2.7 gm. of globulin per 100 cc. of blood. The serum calcium was 10.0 mg. per 100 cc. of blood. The plasma fibrinogen was 0.27 gm. per 100 cc. of blood. The electrophoretic pattern of the plasma proteins was not remarkable except for a slight increase in the beta-globulin fraction. The vitamin C saturation index was within normal limits. The prothrombin consumption test was performed by the method of Ham[8] and was 10.0 seconds with a normal control of 55 seconds. A second determination was 12.5 seconds and a hemophiliac control was 13.0 seconds. Roentgenographic examination of the right wrist, ankle joint and chest was completely negative.

The patient was hospitalized a total of fifteen days. During this period she remained relatively asymptomatic except for the appearance of fresh painful ecchymotic spots over the left leg and the extensor surface of the right elbow. These were very small and disappeared in a few days. Oozing of the lower right gum continued and was still present at the time of discharge.

On the ninth hospital day the patient was started on parenteral cortisone therapy. She received 200 mg. the first day, 150 mg. per day for the next two day and 100 mg. per day on the twelfth and thirteenth hospital days for a total dose of 700 mg. in five days. There was no apparent change in the patient's symptomatology during this period. The patient was discharged unimproved with a coagulation time of over two hours.

An evaluation of the admission hematologic data suggested the probable presence of a circulating anticoagulant in the patient's blood stream. Special studies were undertaken to identify this substance and to study some of its characteristics.

A. Mixture of Patient's Plasma with Normal Blood. The plasma was prepared by mixing sodium citrate with whole blood so that the final citrate concentration was 0.25 per cent. The blood was centrifuged at 2,000 rpm for thirty minutes. The plasma was quickly removed and placed in dry test tubes into which 2 cc. of normal fresh unclotted blood was placed and a clotting time performed (after Lozner,[1] modified).

Patient's Plasma (ml.)	Normal Blood (ml.)	Time (sec.)
0.00	2	180
0.01	2	240
0.05	2	240
0.10	2	300
0.20	2	540

This procedure showed that the addition of even minute amounts of our patient's plasma significantly prolonged the coagulation time of normal blood.

B. Mixture of Patient's Blood with Normal Plasma.

Patient's Blood (ml.)	Normal Plasma (ml.)	Time (min.)
2	0.00	Over 60
2	0.01	Over 60
2	0.05	Over 60
2	0.10	Over 60
2	0.20	Over 60

This procedure demonstrated that the addition of normal plasma to our patient's blood did not alter the coagulation time.

C. Mixture of Patient's Plasma and Normal Plasma. Four and one-half ml. of the patient's and of normal blood were each added to 0.5 ml. of 0.1 M potassium oxalate in separate tubes. The bloods were centrifuged at 1,000 rpm for five minutes. The plasmas in varying dilutions were mixed together and a recalcification time performed using 0.1 ml. of the mixture and 0.2 ml. of 0.025 M calcium chloride (after Ham[8]).

Patient's Plasma (ml.)	Normal Plasma (ml.)	Time (sec.)
0.2	0.0	280
0.4	0.1	285
0.1	0.1	290
0.1	0.2	271
0.1	0.4	185
0.0	0.2	135

This procedure revealed that the addition of small amounts of the patient's plasma to normal plasma increased the recalcification time of normal plasma.

*D. Mixture of Patient's Plasma with Varying Amounts of Normal Plasma and a Hemophiliac's Plasma.**

Normal Plasma (%)	Patient's Plasma (%)	Hemophiliac Plasma (%)	Time (sec.)
100	...	..	44.5
80	20	..	70.0
50	50	..	87.0
20	80	..	93.0
...	100	..	122.0
20	...	80	54.0
80	...	20	50.0
...	20	80	132.0
...	80	20	125.5

The addition of varying percentages of the patient's plasma to normal plasma and hemophiliac plasma demonstrated a similar anticoagulant effect.

E. Titration of Salmine Sulfate† in vitro. Two milliliters of the patient's blood was mixed with varying dilutions of salmine sulfate.

Salmine Sulfate (mg.)	Patient's Blood (ml.)	Time (min.)
0.001	2	Over 60
0.100	2	Over 60
0.000	2	Over 60

F. Titration of Salmine Sulfate in vivo. Fifty mgm. of salmine sulfate was administered to our patient intravenously and her coagulation time was followed.

Time after Salmine Sulfate Administered	Clotting Time (min.)
Control	Over 60
15 minutes	Over 60
60 minutes	Over 60

These two procedures revealed that the addition of salmine sulfate both *in vivo* and *in vitro* had no effect on the patient's clotting time.

G. Effect of the Transfusion of 500 cc. of Whole Blood.

Amount of Blood Administered (ml.)	Clotting Time (min.)
0	Over 60
100	Over 60
500	Over 60

The transfusion of 500 ml. of normal fresh whole blood into our patient had no appreciable effect on her coagulation time.

These procedures indicated the presence of an anticoagulant in the patient's plasma. This effect was not neutralized by the addition of normal blood *in vitro* and *in vivo*, by normal plasma *in vitro* and by salmine sulfate *in vivo* and *in vitro*. On the other hand, the addition of our patient's blood or plasma to normal blood, normal plasma and hemophiliac plasma increased the clotting time of these solutions to an appreciable extent.

Having identified the presence of an anticoagulant we then proceeded to study some of its physical characteristics.

Effect of Heat. The patient's plasma was heated for ten minutes at 57°C. The heated plasma was mixed with varying dilutions of normal plasma and a recalcification time was performed using 0.2 ml. of 0.025 M $CaCl_2$.

Patient's Plasma (ml.)	Normal Plasma (ml.)	Recalcification Time (sec.)
0.1	0.1	540
0.0	0.2	135

Heating had no effect on the anticoagulant properties of the patient's plasma.

Effect of Standing at Room Temperature. The patient's blood was drawn, mixing 0.5 ml. of 0.1 M potassium oxalate with 4.5 ml. of blood. The blood was centrifuged at 2,000 rpm for thirty minutes and the plasma was quickly

* The authors wish to express their appreciation to Dr. Murray Weiner for having performed this test for us in his laboratory.

† Protamine sulfate, 1%, Eli Lilly and Company.

separated from the red cell layer. It was then allowed to stand at room temperature (30°C.) for forty-eight hours. The patient's plasma was then mixed with normal plasma and a recalcification time was performed using 0.2 ml. of 0.025 M $CaCl_2$.

Patient's Plasma (ml.)	Normal Plasma (ml.)	Recalcification Time (sec.)
0.1	0.1	230
0.0	0.2	120

After standing at room temperature of 30°C. for forty-eight hours the anticoagulant effect of the patient's plasma persisted.

Effect of Dialysis. Ten ml. of the patient's plasma was dialyzed against 190 ml. of 21 per cent sodium sulphite until equilibrium was reached. The contents of the dialysis bag was centrifuged and the supernatant containing the albumin was removed. The precipitate was dissolved in 0.15 M sodium chloride and dialyzed against 0.15 M sodium chloride until free of sulphite. Twenty-four hours later the contents of the bag was removed and mixed with normal plasma and a recalcification time was performed using 0.2 ml. of 0.025 M $CaCl_2$ (after Munro).

Patient's Plasma (ml.)	Normal Plasma (ml.)	Recalcification Time (sec.)
0.1	0.1	158
0.0	0.2	81

The anticoagulant effect of the patient's plasma was not dialyzable.

Having studied some of the physical properties of our anticoagulant we next turned to a short study of some of the possible effects of cortisone therapy upon it. Lee-White clotting times were performed before, during and at the completion of cortisone therapy. The coagulation times remained over sixty minutes in every instance. A prothrombin consumption test was performed at the completion of cortisone therapy and was found to be 11.0 seconds, which was unchanged from the pretreatment levels. Finally, varying dilutions of the patient's and normal decalcified plasma were mixed at the end of cortisone therapy and a recalcification time was performed as follows:

Mixture of Patient's Plasma and Normal Plasma after Cortisone Therapy.

Patient's Plasma (ml.)	Normal Plasma (ml.)	$CaCl_2$(.025M) (ml.)	Recalcification Time (sec.)
0.2	0.0	0.2	960
0.4	0.1	0.4	510
0.1	0.1	0.2	350
0.1	0.4	0.4	180
0.0	0.2	0.2	150

From these data it is apparent that cortisone did not in any way neutralize the anticoagulant effect of the patient's plasma; in fact, it is possible that the reverse may have occurred.

COMMENTS

In two recent reviews[9,10] Quick summarizes what appears to be the most acceptable theory of blood coagulation to date. According to this concept five primary agents are required for the formation of thrombin. They are platelet factor, thromboplastinogen, calcium, labile factor and prothrombin. The first two are the thromboplastin factors and when either is deficient or their effect neutralized, poor consumption of prothrombin results during clotting. The latter three constitute the prothrombin complex. The hemorrhagic diseases have therefore been divided into two groups: the hypoprothrombinemias and the hypothromboplastinemias. By means of two simple tests, the prothrombin time and the prothrombin consumption test, a bleeding condition can be initially classified.

When one considers the hemorrhagic diseases associated with hypothromboplastinemia, hemophilia and thrombocytopenic purpura immediately come to mind. In the case of the latter the disease is of at least moderate severity.[11] In very recent years a third condition has been clearly described in which hypothromboplastinemia is prominent. This disease, in many ways quite similar to hemophilia but actually totally unrelated except when they occur together, is due to the presence of a circulating anticoagulant in the blood stream. All three of these conditions have clinical and hematologic similarities, which is not too surprising when one understands the nature of the respective deficiencies in the clotting mechanism. By the same token, however, there are striking differences.

Hemophilia is due to a lack of thromboplastinogen. Because of this lack little thrombin can be formed irrespective of the excess of the other clotting factors. In thrombocytopenic purpura of appreciable severity there is also a defective production of thrombin. In this instance the basic deficiency is lack of platelet factor, not of thromboplastinogen.

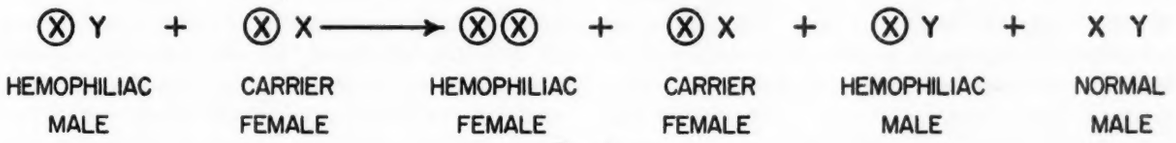

FIG. 1.

In the third condition, namely, hypothromboplastinemia due to a circulating anticoagulant, there is neither a deficiency of platelet factor nor of thromboplastinogen. It is the opinion of most of the authors who have reported their experience with this condition that while the plasma level of circulating thromboplastinogen is probably not altered, its effectiveness is neutralized to a marked degree by the presence of an inactivating antibody. The antibody and the anticoagulant are most probably one and the same.

In all three conditions, hemophilia, thrombocytopenic purpura and circulating anticoagulant, there is a resultant deficiency in thromboplastin.

The coagulation times of our patient varied from 60 to 120 minutes in the presence of a normal platelet count, negative Rumpel-Leedes test, normal bleeding time, normal prothrombin time, negative sternal marrow, normal serum calcium and fibrinogen level. The prothrombin consumption time was markedly decreased, indicating very poor utilization of prothrombin under conditions in which the normal process of clotting was allowed to reach completion. We can presume, therefore, that a deficiency of thromboplastin exists and that we are dealing either with true hemophilia or with a circulating anticoagulant. The patient obviously does not meet any of the basic criteria for the diagnosis of thrombocytopenic purpura.

The syndrome of prolonged clotting time in a female associated with normal hematologic findings and a negative family history has been termed pseudohemophilia,[12] heme-hemophilia[9] and hemophilia-like disease[7] in the literature. Bullock and Filds[13] surveyed 600 hemophiliac families and could find no evidence of the disease among female subjects. Quick[14] reviewed seventy-eight hemophiliac families and could not find any affected females. Bucura[15] collected 197 cases of supposed female hemophiliacs from the literature but found that to none of them did the diagnosis truly apply. Israels[16] in 1951 presented the first substantiated case of hemophilia in a female. In this instance the father and maternal uncle were known hemophiliacs and the patient had suffered from a severe bleeding tendency from childhood. There is but one possible mechanism for the development of hemophilia in the female. (Fig. 1.) One can easily see that, statistically speaking, the required combination of afflicted ancestry must be extremely rare. It should be apparent from what has been presented that, in a female, the diagnosis of hemophilia is untenable when a family history of the disease cannot be substantiated. In retrospect we can presume that some of the cases presented as hemophilia-like syndromes in the literature may have been due to a circulating anticoagulant, as in our case. The adoption of loose terminology to describe this condition and associate it with hemophilia, being both confusing and hematologically incorrect, should be discontinued.

The studies undertaken to identify the presence of an anticoagulant in our patient's blood confirmed our original suspicions. Our patient's blood and plasma when mixed with normal blood, normal plasma and hemophiliac plasma distinctly increased the clotting time of these fluids to an appreciable degree. These determinations indicate that our patient had an anticoagulant or anticoagulant-like substance in her plasma. On the other hand, the addition of normal plasma or blood to our patient's blood or plasma did not effect any change in the coagulation time, proving that she did not have hemophilia. Prolongation of the clotting time of normal blood or plasma upon the addition of similar body fluid from a suspected patient is pathognomonic of the presence of a circulating anticoagulant.

The physical properties of the anticoagulant in our case were similar in most respects to the

great majority of those previously described and studied.[7] The anticoagulant present was not heparin or a heparin-like substance since the addition of salmine sulfate, both *in vitro* and *in vivo*, had no effect on the clotting time. This was the experience of all authors who studied this property of their anticoagulant with one exception.[17] Our anticoagulant had the following additional properties: it was thermostabile, it was not dialyzable and its effect was not dissipated after standing at room temperature for forty-eight hours. Harrington and his associates,[18] studying the properties of antithromboplastin, found that it was made ineffective by dilution, heating at 65°C. for five minutes and by standing at room temperature. We can therefore infer that our anticoagulant was not an antithromboplastin. Further studies of the nature of this anticoagulant showed that it was not an antithrombin and most probably was an antithromboplastinogen. The anticoagulant probably exerts its effect by neutralization or destruction of the thromboplastin-precursor, thromboplastinogen. The anticoagulant in our case and in eleven similar cases did not seem to be a part of the normal mechanisms for maintaining fluidity and coagulability of blood. If it were a foreign substance, which we and many of the previous authors suspect, it would be entirely reasonable to believe that it might well be an antibody. In other instances[19,20] in which the plasma was separated electrophoretically, it was found that the anticoagulant was associated with the gamma globulin fraction. Identification with gamma globulin suggests that the anticoagulant is of the nature of an antibody. Craddock and Lawrence[20] then went further and were able to obtain precipitins in good titer against antihemophiliac globulin (thromboplastinogen). Their evidence strongly suggested that the anticoagulant was an antibody. Dreskin and Rosenthal,[7] although not able to demonstrate either precipitins or complement fixing antibodies to their anticoagulant, nevertheless believed that the immunologic nature of the anticoagulant was highly probable.

As already mentioned, anticoagulants develop in three types of cases; (1) *de novo*, (2) after repeated transfusions of whole blood and (3) in the postpartum state. One cannot formulate any opinion as to why an antibody should develop spontaneously. However, in the latter two categories, which make up the majority of the cases, mechanisms for producing isoimmunization against thromboplastinogen are apparent. Introduction of foreign protein with repeated transfusion of whole blood is an obvious potential cause for the production of antibodies. In three previous cases and in our case the anticoagulant developed within a short interval of parturition. In these women isoimmunization could have occurred across the placental barrier, as with the Rh factor. In our case there is also the history of a retained placenta. In all cases once the transfusion of whole blood had been instituted to correct a bleeding phenomenon, isoimmunization can become accentuated if already present, or it may initially develop. The failure of hemophiliac patients to respond to fresh blood transfusions due to the development of a circulating anticoagulant has been described in the literature.[4,5] In fact this constitutes the largest single group of cases reported in whom an anticoagulant has been identified. When one considers the mechanism for development of the anticoagulant in this type of case, one comes to realize that repeated transfusions is the only pertinent factor. We believe that the development of a circulating anticoagulant and consequent alteration in clinical course can occur in any patient exposed to repeated whole blood transfusions and that when a patient receiving frequent transfusions has a striking alteration in the expected clinical course, with accentuation or initial development of hemorrhagic manifestations, the presence of a circulating anticoagulant must be seriously considered.

Having decided that our anticoagulant was probably an antibody which affected neutralization or destruction of the thromboplastin-precursor, thromboplastinogen, the next logical step was to treat our patient with cortisone or ACTH. Smith and his co-workers[21] studied the effects of ACTH and cortisone on certain factors of blood coagulation as a corollary to treating twenty-six patients with various collagen diseases. Their results were variable and did not allow of any general conclusions. In some patients the clotting times were increased presumably because of the release of heparin or a heparin-like substance due to a situation "akin to the hyperheparinemia of anaphylactic shock." In others there was a striking decrease in the clotting time in less than twenty-four hours. In our own patient there was no change in the clinical course which would suggest any beneficial effect. Indeed, the patient had an exacerba-

tion of symptoms and objective findings which continued during the follow-up period. This reached its height three months after discharge from the hospital when the patient had a second massive gastrointestinal hemorrhage.

CONCLUSIONS

1. A case of a twenty-seven year old female is presented who, three months postpartum, developed a circulating anticoagulant associated with a striking hemorrhagic diathesis. A prolonged coagulation time and markedly decreased prothrombin consumption time were the prominent hematologic findings.

2. The anticoagulant was probably an antithromboplastinogen ultimately causing either neutralization or destruction of the thromboplastin-precursor.

3. Isoimmunization via the placental site was a likely cause for the development of this anticoagulant. Transfusion of whole blood, which became a therapeutic necessity once the patient began to bleed, may have accentuated the anticoagulant effect.

4. Cortisone therapy did not favorably alter the clinical or hematologic picture and may have accentuated the condition.

5. The adoption of terminology that associates hemophilia and circulating anticoagulant is confusing and hematologically incorrect and should be discontinued.

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Tuberous Sclerosis*

Report of a Case with Unusual Pulmonary Manifestations

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THE triad of adenoma sebaceum, mental retardation and convulsions points to the diagnosis of tuberous sclerosis. This is a rare disease characterized by a tendency to tumor formation with a predilection for the skin, brain and eye, although practically every organ in the body has been reported to be involved at times. Clinical manifestations usually become obvious in childhood and the majority of these patients are found in mental institutions. In the absence of the classic triad the multiplicity of organ involvement may produce clinical pictures which present considerable diagnostic difficulty.

The following case is believed worthy of reporting because neuropsychiatric symptoms were absent and involvement of the respiratory system was the most striking clinical finding. In this twenty-three year old woman asymptomatic "miliary" lesions in the lung of three years' known duration were followed by recurrent spontaneous pneumothorax and death within one year. Since we have not encountered a similar American case report, both the European and American literature pertaining to pulmonary tuberous sclerosis have been reviewed.

CASE REPORT

M. H., a twenty-five year old colored maid, entered the hospital on September 24, 1951, complaining of dyspnea associated with right-sided chest pain and cough. Six hours before the onset of these symptoms she had been struck on the right side of the chest by her husband.

This was the patient's third hospital admission. In June, 1949, she had been admitted to the Gynecology Service because of hypermenorrhea and anemia due to a leiomyoma of the uterus. At that time she was noted to have "neurofibroma-like warty growths" on her face and body. Physical examination revealed moist rales at both apices. The patient gave a history of occasional dyspnea for one year and had coughed up a small amount of blood. A chest roentgenogram showed small miliary densities throughout both lung fields, more marked in the bases. (Fig. 1.) There was no evidence of hilar adenopathy, pleural effusion or cardiac enlargement. The patient had no fever and little cough. Sputum studies failed to reveal acid-fast bacilli. She was discharged without operation to be followed in the outpatient department while the etiology of the pulmonary findings was being determined.

During the next six months diagnostic studies failed to demonstrate the presence of tuberculosis. Sputum studies were negative, tuberculin skin tests were negative and there was no change in the chest roentgenogram. Furthermore, the patient was asymptomatic and gained weight. The presumptive diagnosis was changed to sarcoidosis. Roentgenograms of hands and feet at this time were negative.

The patient continued to have hypermenorrhea with moderate anemia and in June, 1950, she was readmitted for hysterectomy. The physical, laboratory and radiographic findings were, with one exception, unchanged. She had a low-grade fever and evidence of a urinary tract infection with albuminuria, a few red and white blood cells in the urine and a urine culture positive for Aerobacter aerogenes. She was treated with sulfadiazine and streptomycin with disappearance of the cellular elements but persistence of albuminuria. An intravenous urogram appeared normal except for the suggestion of a possible mass located in the lower pole of the left kidney. A consultant from the Department of Internal Medicine concurred with the pre-

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sumptive diagnosis of sarcoidosis and thought the patient also had neurofibromatosis. Total hysterectomy was performed and leiomyomas of the uterus were found. Histologic examination revealed proliferative endometrium and an endometrial polyp. The patient was discharged August 29, 1950, and was asymptomatic until the present admission.

The patient had seven siblings, all of whom were said to be normal. Physical examination and chest roentgenograms of the mother and two sisters were normal.

The nodules on the patient's face and body had been present since the age of nine months. At five years of age she had a series of grand mal seizures over a period of two months, which ceased after short-term administration of anticonvulsant treatment. Since that time she had had no convulsions nor had she taken any drugs. She seemed above normal in intelligence and had completed high school.

Physical examination on the present admission revealed a markedly dyspneic and orthopneic young colored woman. The temperature was 98°F., pulse 94, respirations 30 and blood pressure 130/70. Several areas of depigmentation were noted on all extremities. There was a 1 by 1 by 5 cm. firm, movable, subcutaneous nodule in the center of the scalp just within the hairline. There were numerous skin lesions of the face, none involving the circumoral region. On the forehead were several brownish-pink, soft, slightly raised nodules varying in size from 2 cm. to 1 mm. There was a "butterfly distribution" of lesions, pedunculated and plaque-like, round, pink to brown and varying in size from 0.25 cm. to pinhead, and similar lesions were present on the chin. Several of these same lesions were scattered over the body. Along the sixth right rib in the anterior axillary line was a 1 by 2 by .5 cm. firm, movable, subcutaneous nodule.

Funduscopic examination showed a flat, grey, avascular area just below the inferior temporal artery on the left involving the superficial retinal layer, which was interpreted as a phacoma by the ophthalmologic consultant.

Examination of the chest revealed signs of pneumothorax on the right. The left lung was clear to percussion and auscultation. The heart was not remarkable. Abdominal and pelvic examinations were normal except for absent uterus. The neurologic examination was normal. Examination of the extremities revealed

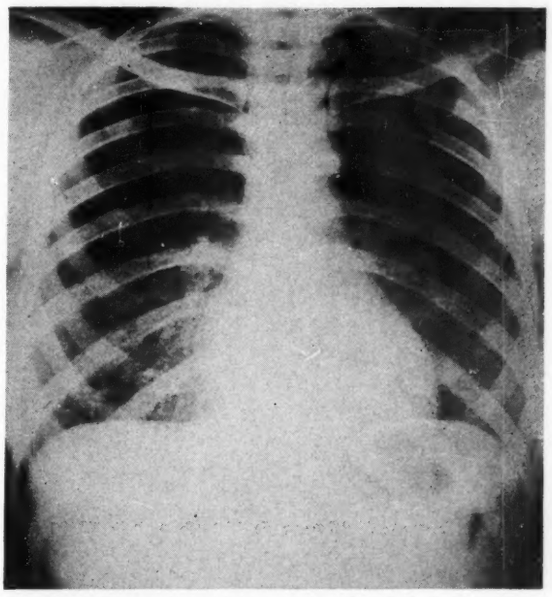

FIG. 1. Chest roentgenogram showing bilateral miliary densities.

no edema or clubbing. The toes showed several subungual fibromas.

Urinalyses showed a normal specific gravity with proteinuria varying from 3+ initially to a trace when the patient was discharged. There were no cellular elements or casts. The hemoglobin value on admission was 8.2 gm. per 100 cc. This rose to 11.1 gm. following iron therapy and proper diet. There was no leukocytosis. Sickle cell preparations were negative and stool specimens showed no evidence of occult blood. Bone marrow examination was normal. Blood urea nitrogen was 10 mg. per cent. Phenolsulfonphthalein excretion was 45 per cent in one hour. Serologic test for syphilis and skin test for tuberculosis were negative. An electrocardiogram and electroencephalogram were normal.

The chest roentgenogram confirmed the presence of an almost complete pneumothorax on the right side. (Fig. 2.) Further radiographic studies demonstrated the presence of intracranial calcifications, sclerotic lesions of bone and multiple renal tumors. (Fig. 3.)

Several biopsies of the skin lesions were made. The opinion was that "the general pattern of the skin lesions from this patient are consistent with some of the dermal manifestations of tuberous sclerosis."

The combination of clinical, roentgenologic and pathologic findings made clear the diagnosis of tuberous sclerosis.

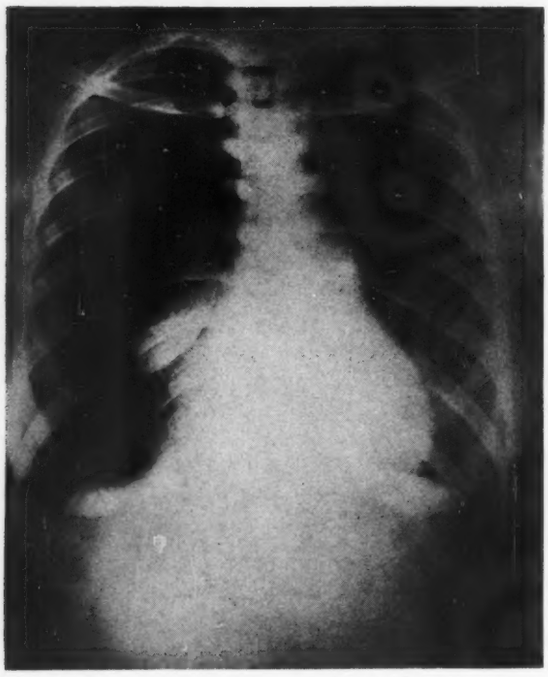

FIG. 2. Chest roentgenogram on third admission showing complete right pneumothorax.

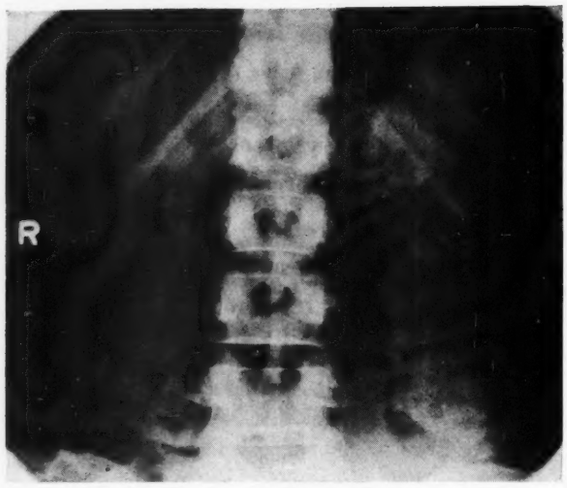

FIG. 3. Intravenous nephrogram showing enlargement of both kidneys with masses in the lower pole of both kidneys. The entire kidneys are opacified with the contrast medium, indicating that the tumors have a satisfactory blood supply.

The pneumothorax was treated conservatively with aspiration of 1,500 cc. of air immediately after admission and the lung re-expanded without complications.

After discharge the patient did well but was readmitted three times with spontaneous pneumothorax involving either side, the last admission being in August, 1952. On the morning of December 23, 1952, while at home, she complained of sudden chest pain and severe shortness of breath and died within two minutes. No autopsy was obtained.

COMMENT

We have found only two clinically studied and pathologically proved cases of pulmonary involvement in tuberous sclerosis reported in the European literature.[1–3] These are surprisingly similar to the present one in that the respiratory symptom of dyspnea and the chest roentgen findings were the chief clinical manifestations of tuberous sclerosis, and the onset of symptoms occurred in adult life.

In both of these cases basic histopathologic changes are described as (1) diffuse transformation of the alveoli and bronchioles into small cavities or cystic dilatations and (2) thickening and hyperplasia of the septa which form the walls of these cysts. The overgrowth involves connective tissue, muscle and vessels in varying degree. The muscle elements may predominate sufficiently for the stroma to be classified as "diffuse myomatosis" by the pathologist. This curious form of generalized cystic disease of the lung is not related to "congenital cystic disease" since the cysts generally do not communicate with the bronchial tree.

The cysts have a tendency to increase in size from bare visibility (approximately 2 to 3 mm.) to "the size of hazel nuts or larger."[2] In Samuelsen's case the largest cyst was 1 cm. in diameter. The cysts may be multangular and the interstitial strands of varied thickness.

If the cysts appear small and uniform, as in the case here reported, they do not appear as obvious cystic areas on the roentgenograms. Instead, the fine, round striae which separate the cysts show up as a reticular pattern throughout the lung. The points of intersection of this honeycomb structure may have a slightly nodular appearance so that the lung fields radiographically simulate miliary tuberculosis, pneumoconiosis, sarcoidosis and other disseminated lesions. (Fig. 4.)

Berg and Zachrisson[1] reported lung changes in two sisters who had been in good health until the age of thirty. These two women had had adenoma sebaceum and fibroma unguinale since childhood but neither had had any manifestation of pulmonary, mental or neurologic disease. One sister was admitted to the hospital because of a spontaneous pneumothorax. The cystic

changes on the chest roentgenogram showed the previously described variation and later increased in size. After discharge from the hospital "the subject's condition alternated between periods of pneumothorax and, to all appearances, perfect health." There was no cough or expectoration. The patient developed gradually increasing dyspnea and cor pulmonale and died two years after her first admission.

Vejlens,[2] who performed the necropsy, gave the first detailed report on the pathologic findings in the lungs and designated these as "tuberous sclerosis of the lungs." He regarded the "myomatosis" as "one of the many expressions of a malformational disease with a tendency toward tumor formation." Autopsy also revealed tuberous sclerosis of the brain, multiple bilateral renal and pararenal tumors, a splenoma and a lymph gland myoma.

The sister of this patient complained of moderate dyspnea while working. Her chest roentgenogram showed a "slender reticular pattern over both lung fields caused by numerous dense round translucencies up to the size of peas." A roentgenogram one year later showed no change. A bronchogram was normal. In addition to the skin lesions the sister had a tumor of the ocular fundus and a rectovaginal myoma. Two brothers also showed stigmata of tuberous sclerosis but had normal chest roentgenograms.

The second autopsied case[3] was that of a forty-nine year old woman who had been treated for "chronic miliary tuberculosis" in a sanitorium over a five-year period because of the "characteristic" miliary appearance of the lung fields, along with symptoms of dyspnea, cough, expectoration and fatigue, and elevated sedimentation rate. Cultures and skin tests for tuberculosis were negative. The presumptive diagnosis was subsequently changed to sarcoidosis because of the lack of change in the appearance of her chest roentgenogram and because of roentgen changes in the hands. She had no adenoma sebaceum, and there was no mention of epilepsy. There were evidently mental disturbances since she later had a diagnosis of "imbecility." Her clinical status was complicated by the presence of long-standing rheumatic heart disease and she died of "cerebral infarction and hemorrhage" three years after the clinical diagnosis of "sarcoidosis" was made.

At necropsy the cysts varied from "quite diminutive" to several millimeters in size. The areas of interstitial "myofibrosis," which produced the miliary granular appearance, were about 1 to 2 mm. in size. An element of hemosiderosis contributed to the pulmonary findings. Other autopsy findings included tuberous sclerosis of the brain and multiple benign tumors in both kidneys. Impressed by these pulmonary manifestations, Berg and Zachrisson made the presumptive clinical diagnosis of tuberous sclerosis in a thirty year old male who was seen at the hospital because of a spontaneous pneumothorax. He had previously been in good health except for diabetes insipidus of ten years' duration. Chest roentgenograms, which remained unchanged during the two-year period of observation, showed the changes seen in tuberous sclerosis, with the cysts varying considerably in size. The diagnosis at first entertained was "chronic miliary tuberculosis." The patient remained asymptomatic during a two-year follow-up period. A bronchogram was normal. The radiographic appearance of the chest was unchanged. There were no other clinical stigmata of tuberous sclerosis.

FIG. 4. Detail of lung involvement.

Ackermann[4] also made the presumptive clinical diagnosis of tuberous sclerosis in a twenty-five year old male with similar appearing lungs, who also had diabetes insipidus, polydactyly, and a peculiar multiple osteodystrophy somewhat akin to that seen in neurofibromatosis and unlike that previously described in tuberous

sclerosis. During a six-year period there was no change in the appearance of the lungs.

Since the diagnosis of tuberous sclerosis in these two preceding patients is tenuous, being suggested largely on the basis of the chest findings, the question arises whether these histopathologic changes in the lung have been reported without evidence of other organ involvement and in conditions other than tuberous sclerosis.

Rosendal[5] reported the case of a forty-two year old woman with progressive respiratory insufficiency, including episodes of pneumothorax. Necropsy showed the typical "diffuse myomatosis and cyst formation in the lung" without other clinical or anatomical evidence of tuberous sclerosis or other associated disease. Von Stoessel[6] reported two similar cases, under the description "muscular cirrhosis of the lung."

Until the present time these pulmonary changes have not been reported in conditions other than tuberous sclerosis. However, since the pulmonary lesions are believed to be part of a malformational tumor-forming tendency, one would occasionally expect to encounter these changes in neurofibromatosis and similar malformational processes.

CONCLUSION

Since most of the organ involvement in tuberous sclerosis is asymptomatic, it appears that the respiratory syndrome, although uncommon, is second only to intracranial involvement as a signal symptom of this disease and in its serious import for the patient. It is suggested that other evidence of tuberous sclerosis or other malformation be searched for in patients who present themselves with spontaneous pneumothorax and cystic or "miliary" lung disease.

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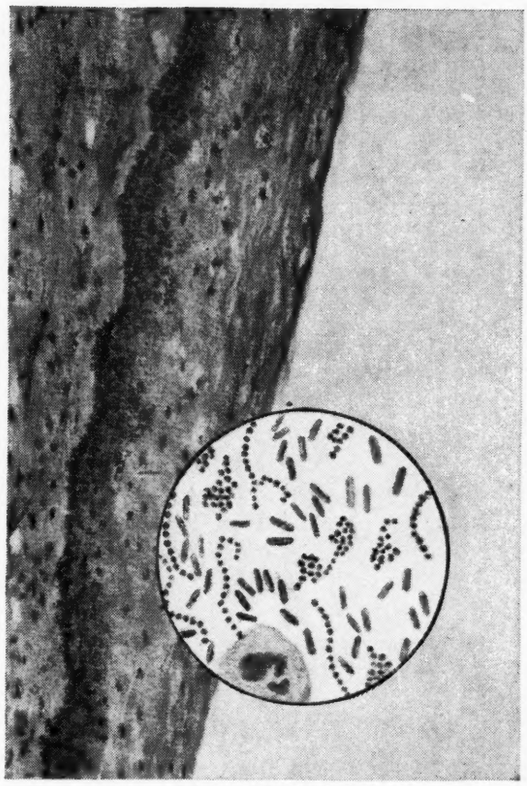
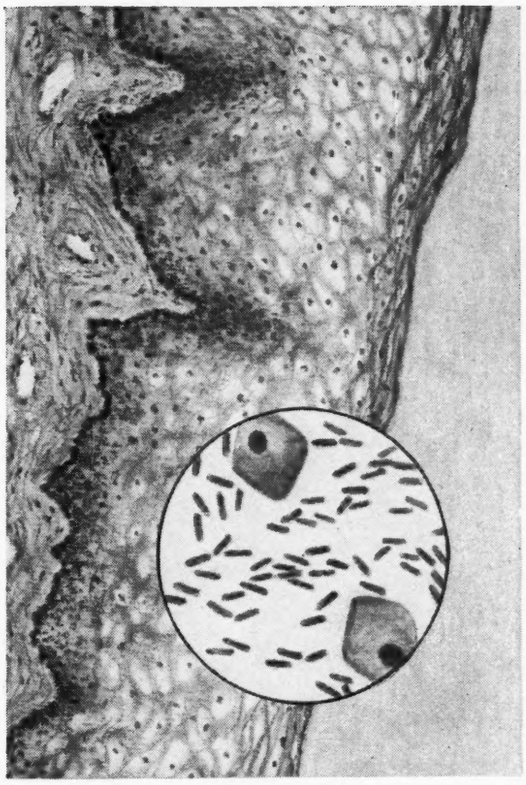


Senile vaginal epithelium is low in glycogen, low in acid and (inset) low in protective Döderlein bacilli, encouraging growth of pathogenic organisms.



Normal vaginal epithelium is high in glycogen, is definitely acid and (inset) contains adequate Döderlein bacilli to combat pathogenic organisms.

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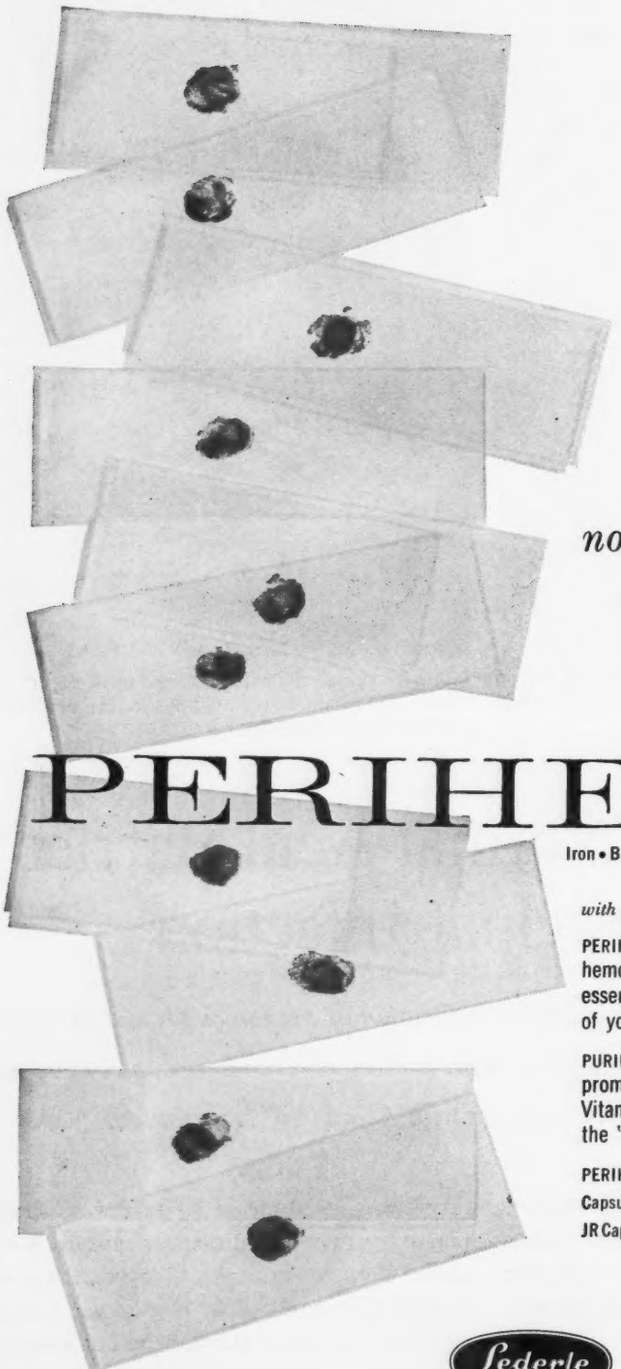

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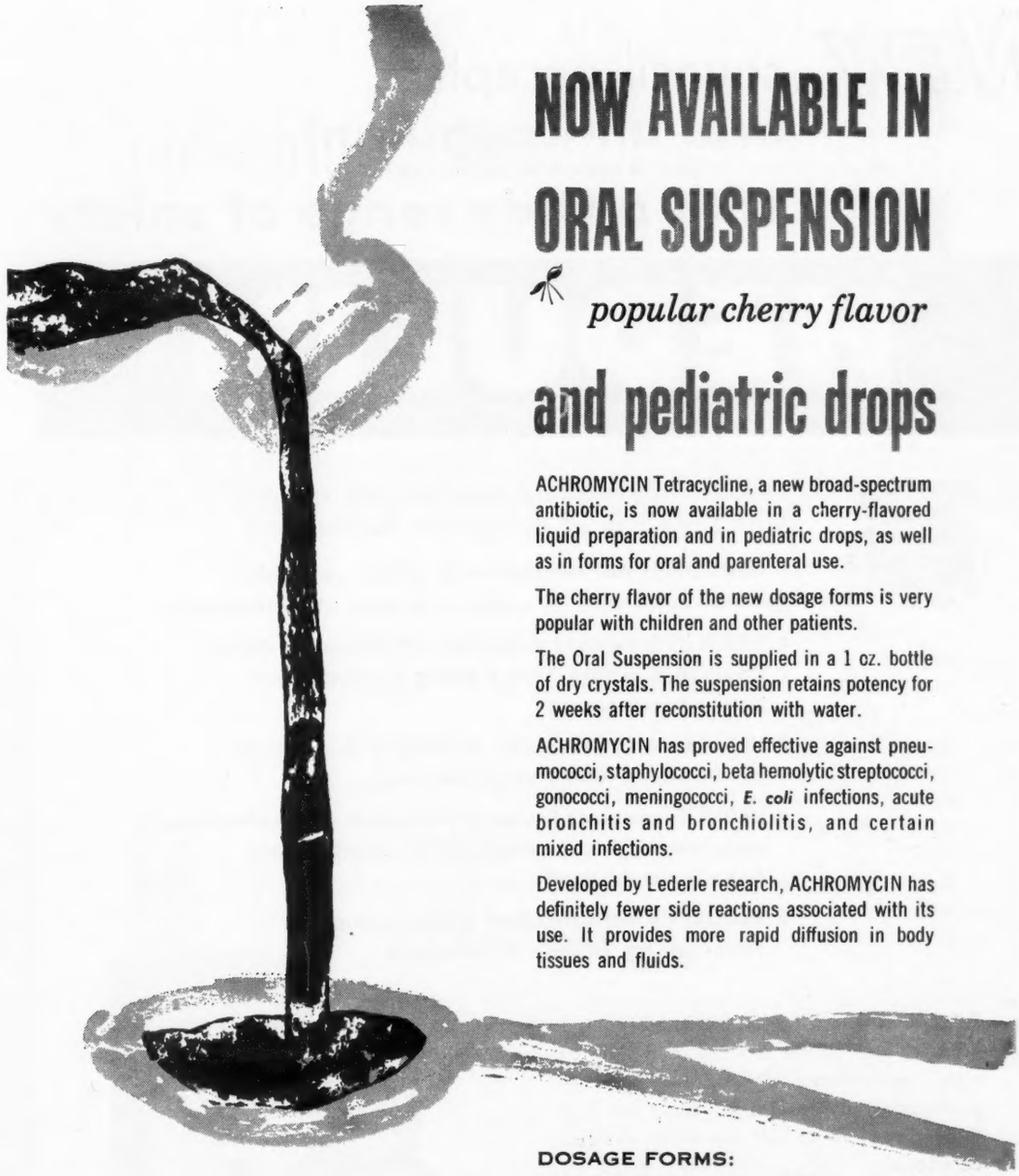

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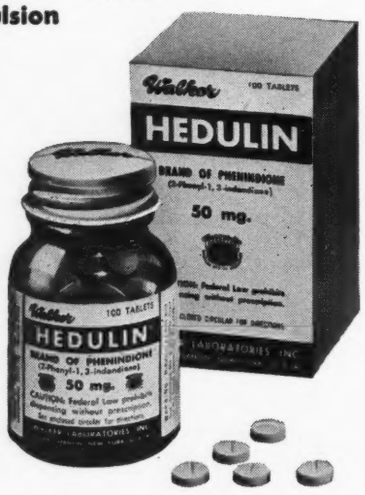

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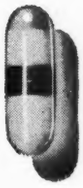

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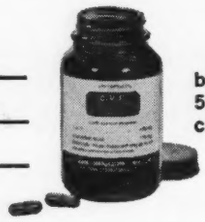

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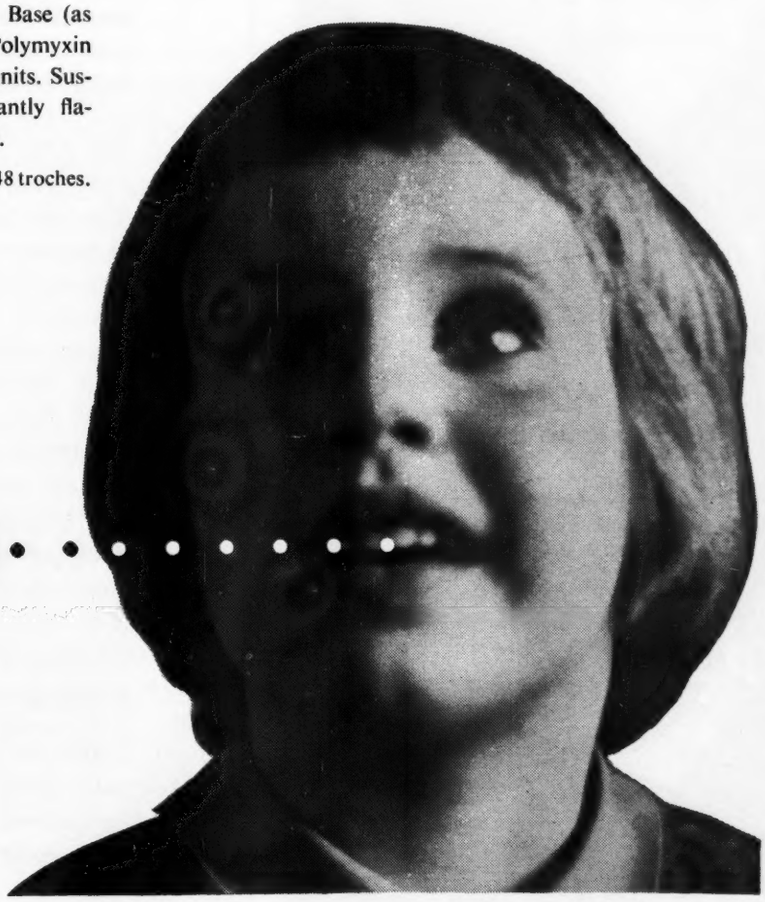

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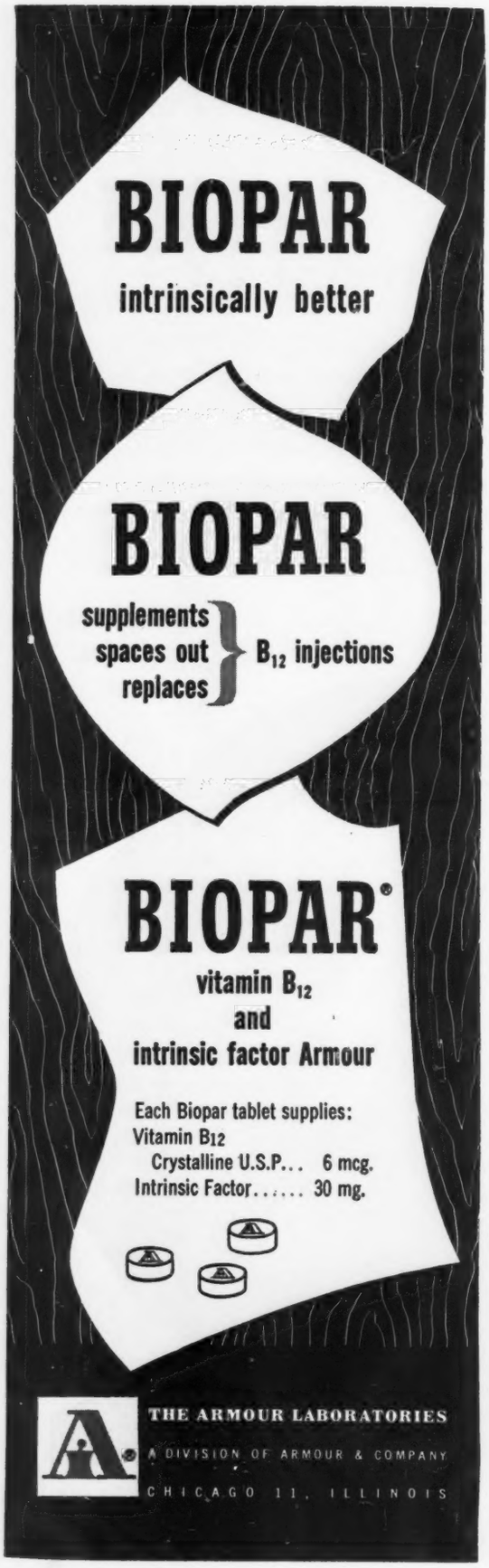

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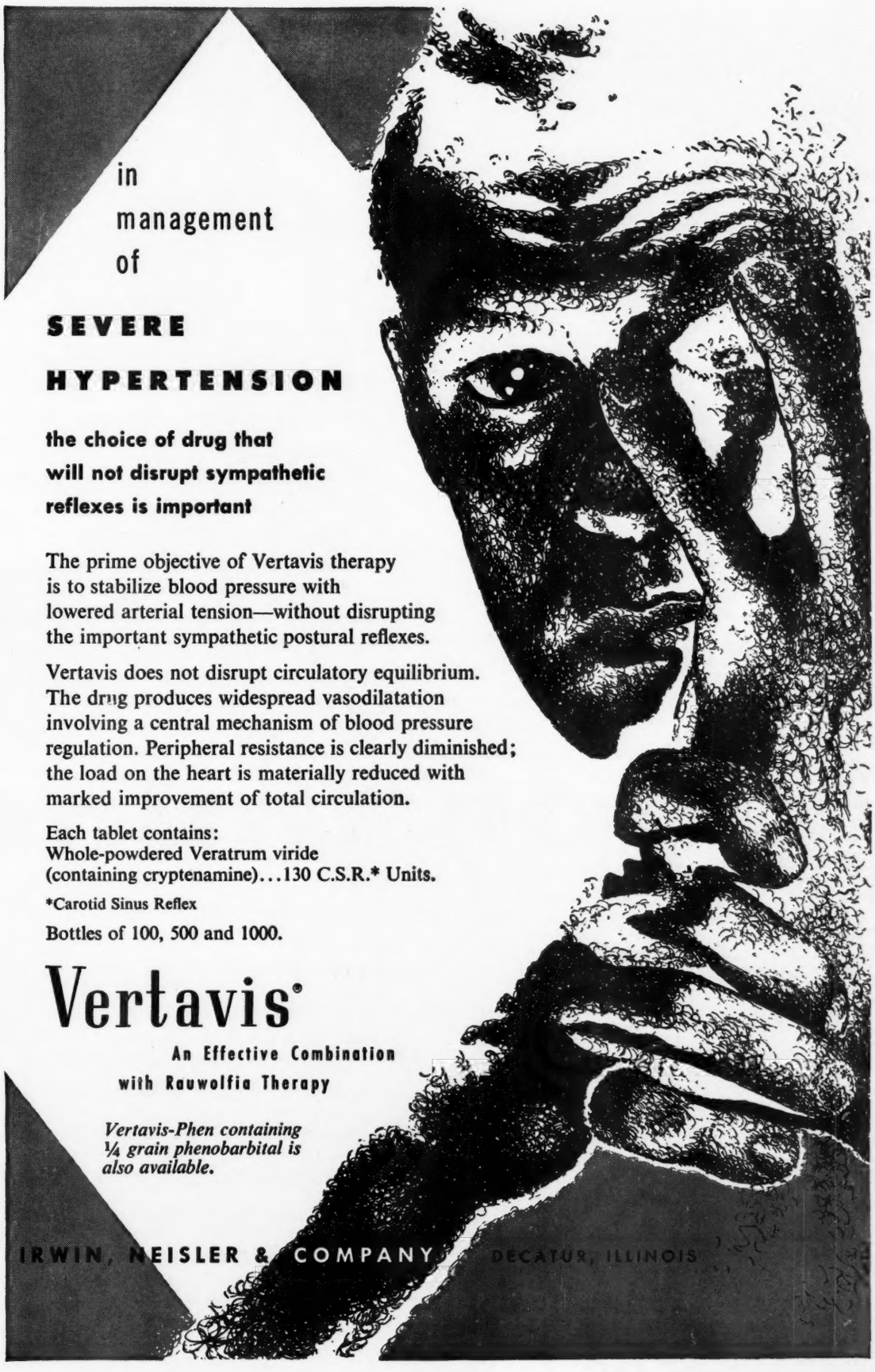

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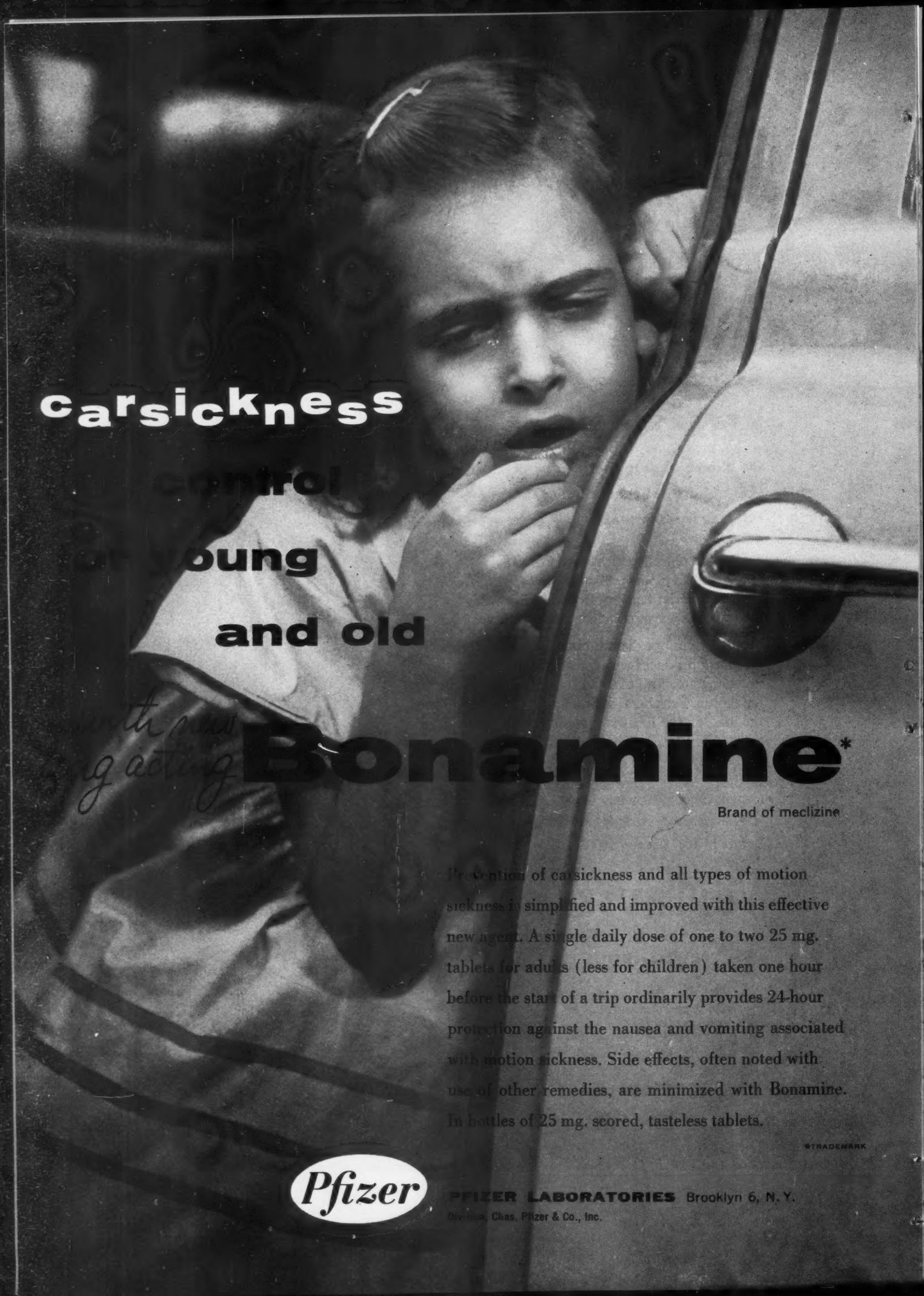

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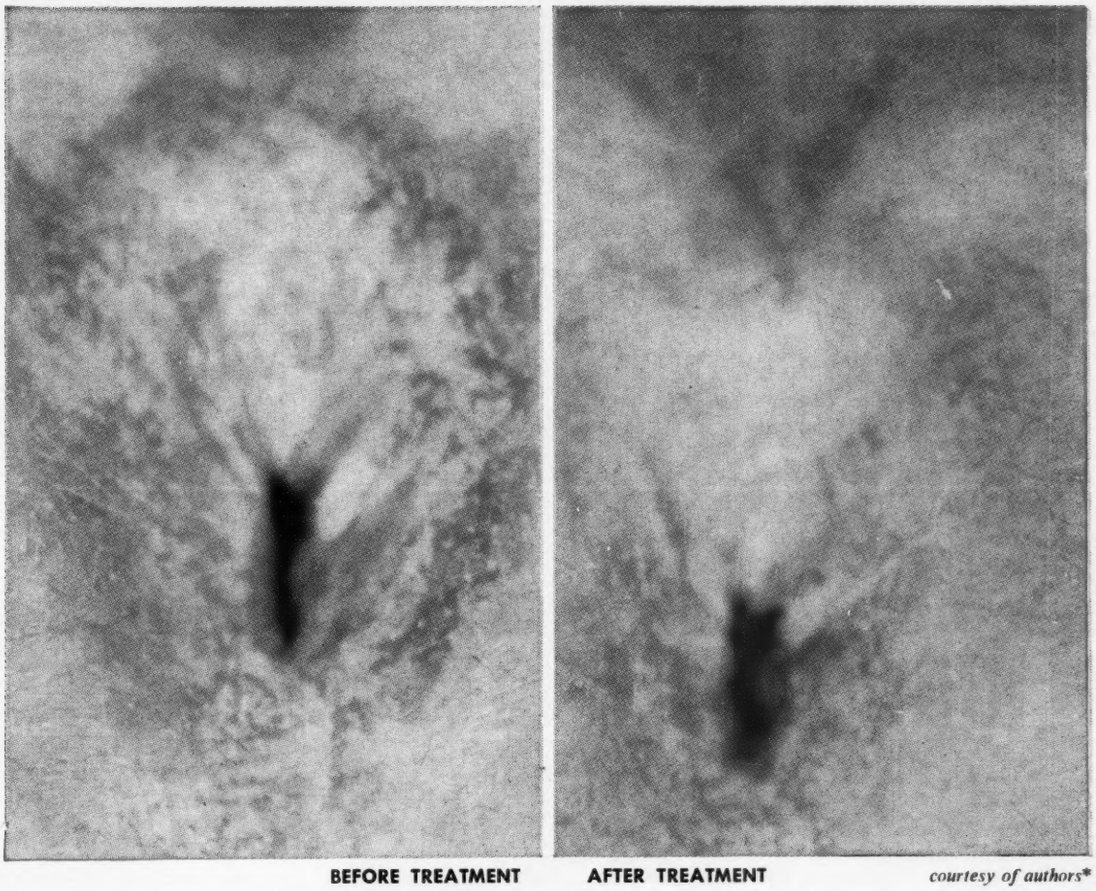

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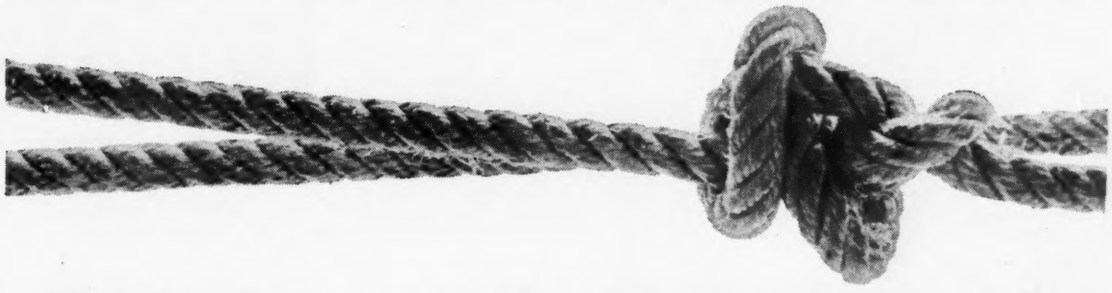

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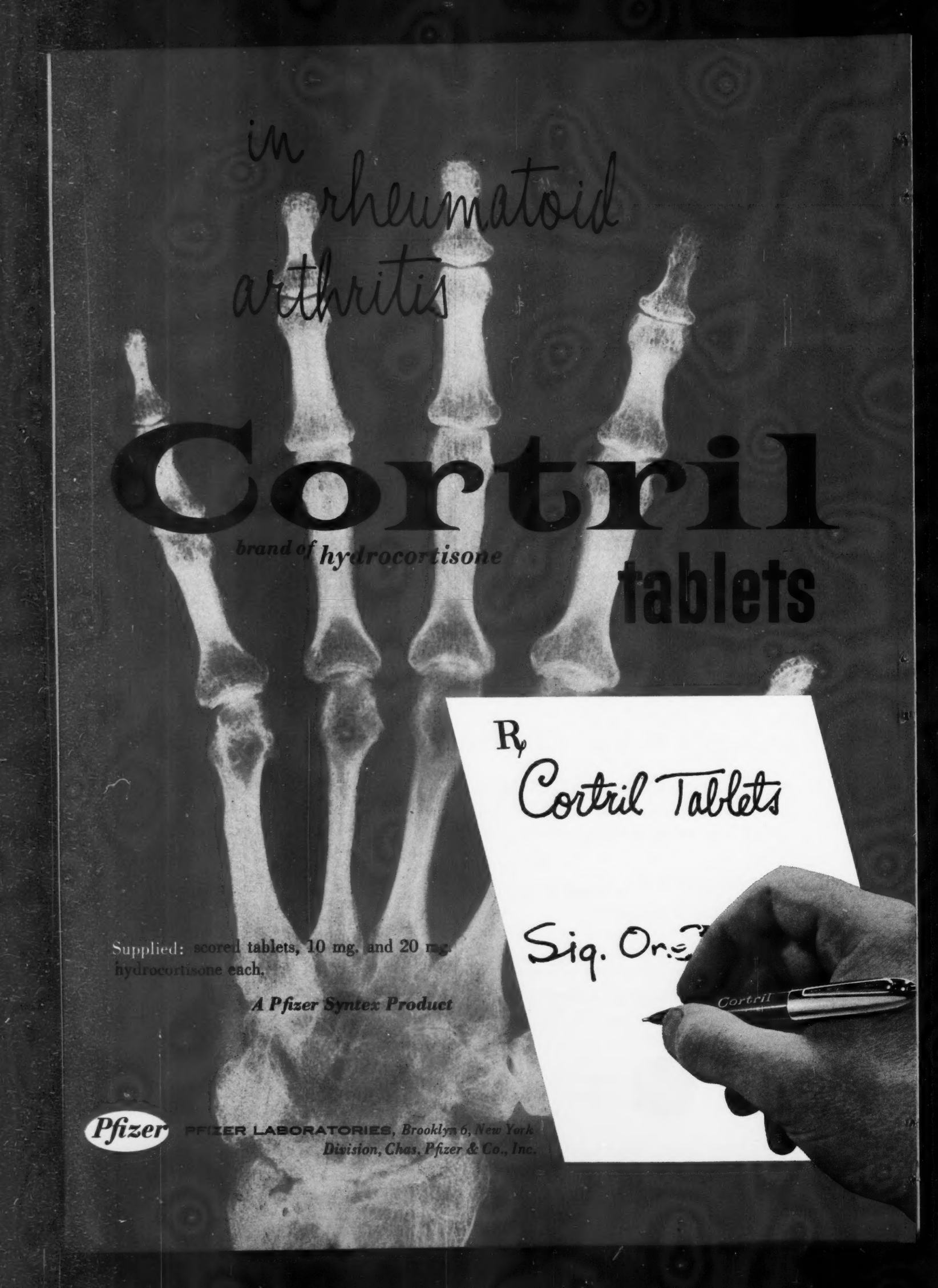
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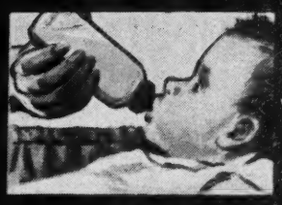

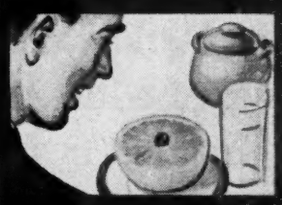

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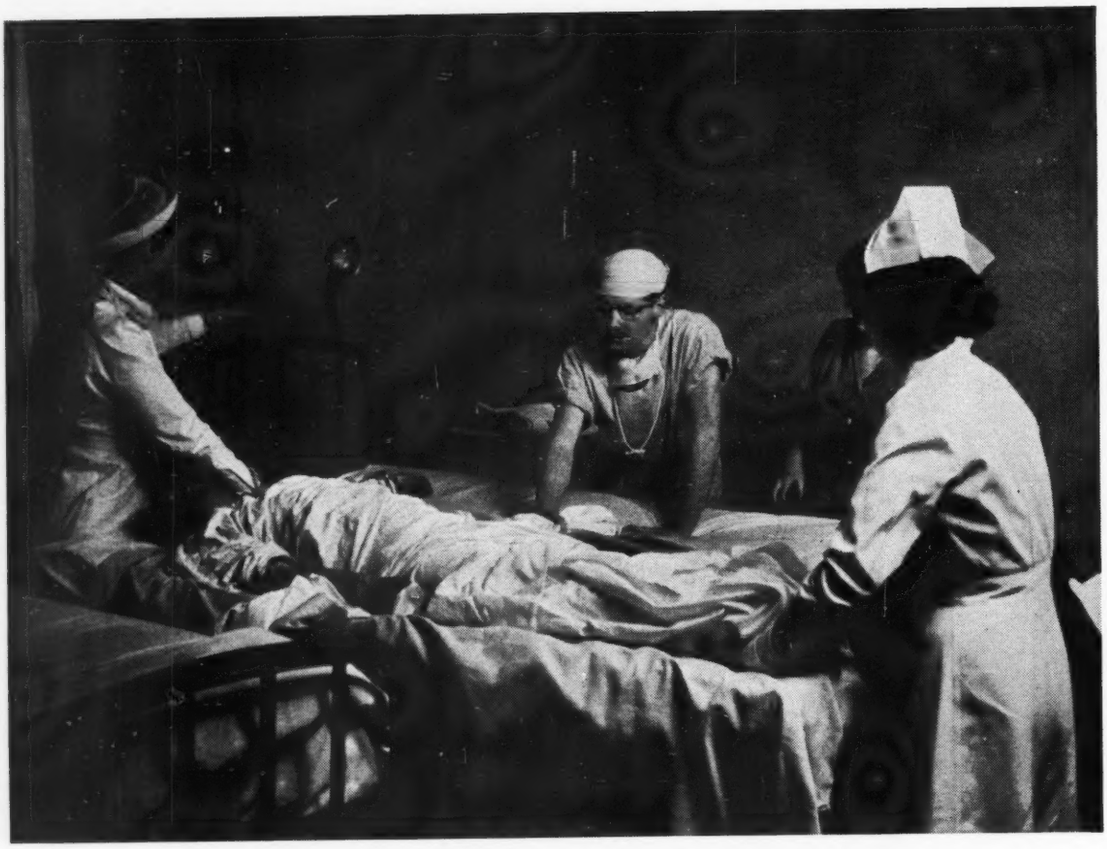

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stress New ASF* *(Anti-Stress Formula)*

BASIC PHARMACEUTICALS FOR NEEDS BASIC TO MEDICINE

536 Lake Shore Drive, Chicago 11, Illinois

Rx OERIG

MORE THAN IRON ALONE may be needed for red blood cell development and maturation. "Bemotinic" supplies all factors known to be essential for maximal hemopoietic and clinical response.

"BEMOTINIC"®

TO SPEED RECOVERY IN THE COMMON ANEMIAS

In addition to the convenient capsule form, "Bemotinic" is also supplied as a liquid — an extremely palatable orange-flavored preparation with no aftertaste, easy to pour, and non-alcoholic.

"BEMOTINIC" LIQUID

Each teaspoonful (5 cc.) contains:

Ferric ammonium citrate	200.0	mg.
Vitamin B_{12} U.S.P. (crystalline)	4.0	mcg.
Extractive as obtained from of fresh gastric tissue	450.0	mg.
Folic acid U.S.P.	0.33	mg.
Thiamine HCl (B_1)	1.5	mg.
Riboflavin (B_2)	1.0	mg.
Pyridoxine HCl (B_6)	0.2	mg.

No. 940 — Bottles of 16 fluidounces and 1 gallon.

SUGGESTED DOSAGE:

Adults: 1 to 2 teaspoonfuls. Children: ½ to 1 teaspoonful. Three times daily, or more as required. Preferably taken with food.

"BEMOTINIC" CAPSULES

Each capsule contains:

Ferrous sulfate exsic. (3 gr.)	200.0	mg.
Vitamin B_{12} U.S.P. (crystalline)	10.0	mcg.
Gastric mucosa (dried)	100.0	mg.
Desiccated liver substance, N.F.	100.0	mg.
Folic acid U.S.P.	0.67	mg.
Thiamine mononitrate (B_1)	10.0	mg.
Vitamin C (ascorbic acid)	50.0	mg.

No. 340 — Bottles of 100 and 1,000.

SUGGESTED DOSAGE:

1 or 2 capsules three times daily. Preferably taken with food.

NEW YORK, N. Y. Ayerst MONTREAL, CANADA

5440

ORAL SUSPENSION: *Cherry flavor. 250 mg. per 5 cc. teaspoonful*

CAPSULES: *250 mg., 100 mg., 50 mg.*

ACHR

now available in these many convenient forms:

TABLETS: *250 mg., 100 mg., 50 mg.*

SPERSOIDS®: *50 mg. per teaspoonful (3.0 Gm.)*
Dispersible Powder

INTRAVENOUS: *500 mg., 250 mg., 100 mg.*

OMYCIN*

Tetracycline HCl *Lederle*

PEDIATRIC DROPS: *Cherry flavor. Approx. 25 mg. per 5 drops. Graduated dropper.*

ACHROMYCIN, the new broad-spectrum antibiotic, is now available in a wide range of forms for oral and parenteral use in children and adults. New forms are being prepared as rapidly as research permits.

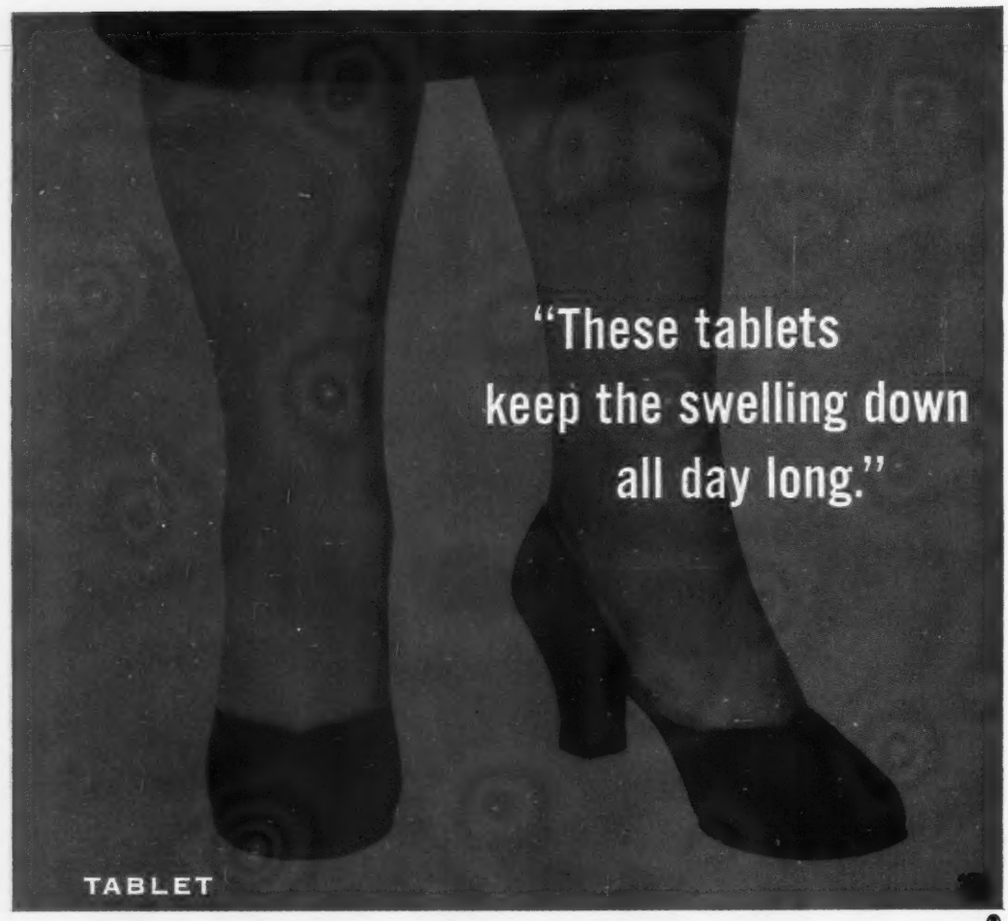
ACHROMYCIN is definitely less irritating to the gastrointestinal tract. It is more rapidly diffusible in body tissues and fluids. It maintains effective potency for a full 24-hours in solution.

ACHROMYCIN has proved effective against beta hemolytic streptococcic infections, *E. coli*, meningococci, staphylococci, pneumococci and gonococci, acute bronchitis, bronchiolitis, pertussis and the atypical pneumonias, as well as virus-like and mixed organisms.

Lederle

LEDERLE LABORATORIES DIVISION AMERICAN Cyanamid COMPANY Pearl River, N.Y.

*Reg. U.S. Pat. Off.



NEOHYDRIN®

BRAND OF CHLORMERODRIN

NORMAL OUTPUT OF SODIUM AND WATER

Individualized daily dosage of NEOHYDRIN -- 1 to 6 tablets a day as needed -- prevents the recurrent daily sodium and water reaccumulation which may occur with single-dose diuretics. Arbitrary limitation of dosage or rest periods to forestall refractivity are unnecessary. Therapy with NEOHYDRIN need never be interrupted or delayed for therapeutic reasons. Because it curbs sodium retention by inhibiting succinic dehydrogenase in the kidney only, NEOHYDRIN does not cause side actions due to widespread enzyme inhibition in other organs.

Prescribe NEOHYDRIN in bottles of 50 tablets. There are 18.3 mg. of 3-chloromercuri-2-methoxypropylurea in each tablet.

Leadership in diuretic research

LAKESIDE LABORATORIES, INC · MILWAUKEE 1, WISCONSIN

PHOTOGRAPH BY RUZZIE GREEN

When carefree eating leads to diarrhea...

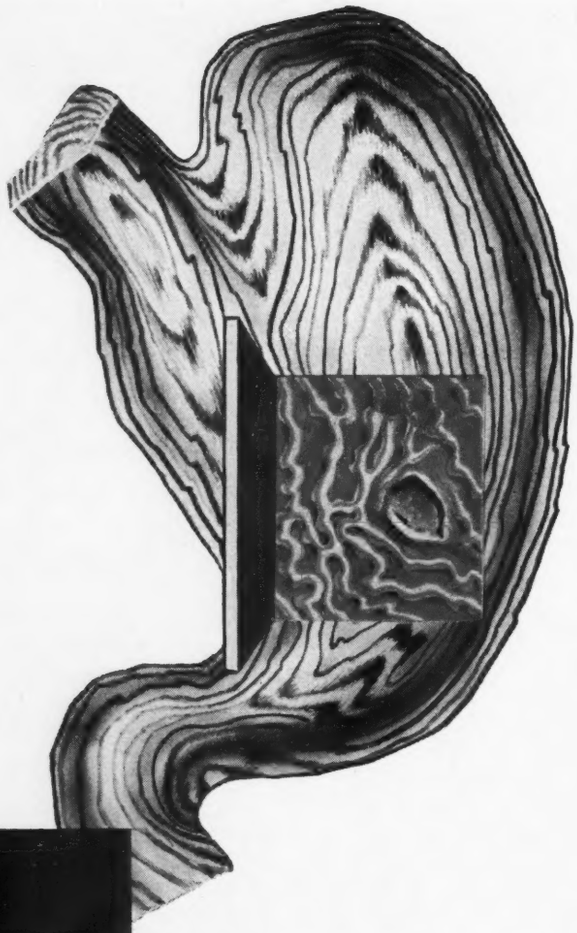
CREMOSUXIDINE®

SULFASUXIDINE® SUSPENSION WITH PECTIN AND KAOLIN

Food contamination is common when the weather turns warmer—may bring diarrhea to your unsuspecting patients.

With palatable CREMOSUXIDINE, you have an exceptionally effective triad for control of specific and non-specific diarrhea: **(1)** 'Sulfasuxidine'—for bacteriostatic action, **(2)** pectin—to inactivate toxins and, **(3)** kaolin—to adsorb intestinal irritants and restore stools to normal consistency. CREMOSUXIDINE is well-tolerated.

Quick Information: Average *adult* dose is 1½ to 2 tablespoonfuls six times a day. *Children* and *infants* in proportion. *Supplied* in Spasaver® bottles of 16 fl. oz.



maalox®

for gastric hyperacidity in peptic ulcer

Suspension MAALOX—Rorer provides the *hydroxides* of Magnesium and Aluminum in colloidal form . . . pleasantly flavored and highly acceptable, even with prolonged use. Relief of pain and epigastric distress is prompt and long-lasting. Freedom from constipation and side effects common to other antacids is noteworthy.

supplied:
in 355 cc. (12 fluidounce) bottles. Also in bottles of 100 tablets. (Each Maalox tablet is equivalent to 1 fluidram of Suspension.)

Samples will be sent promptly upon request.

WILLIAM H. RORER, INC.

Drexel Bldg., Independence Square, Philadelphia 6, Penna.

ESTABLISHED IN 1910

The known clinical advantages of rapid absorption, wide distribution in body tissues and fluids, prompt response and excellent toleration, PROVED by the extensive experience of physicians in successfully treating many common infections due to susceptible gram-positive and gram-negative bacteria, rickettsiae, spirochetes, certain large viruses and protozoa, have established

Terramycin®

Brand of oxytetracycline

as a broad-spectrum antibiotic of choice

PROVED

PFIZER LABORATORIES, Brooklyn 6, N.Y.
Division, Chas. Pfizer & Co., Inc.

Pfizer

NOW: for Adults and Children!

Nephenalin®
(for adults)

Nephenalin®
PEDIATRIC

First, under tongue for quick asthma relief

from aludrine (Isopropyl arterenol) HCl in coating

Then, swallow tablet for prolonged asthma control

from theophylline, ephedrine, phenobarbital, contained in tablet core

NEPHENALIN, the "relay-action" tablet combining two widely prescribed, complementary anti-asthmatics, is now available in two potencies: the familiar square, *purple* tablet for adults, and the smaller square, *red* tablet for children. Since a single NEPHENALIN tablet provides quick asthma relief, thereby often replacing the nebulizer, and since relief lasts about four hours, many asthmatic patients will find it the most convenient and efficient anti-asthmatic they have ever used. Bottles of 20 and 100 tablets.

Thos. Leeming & Co. Inc. 155 East 44th St., New York 17